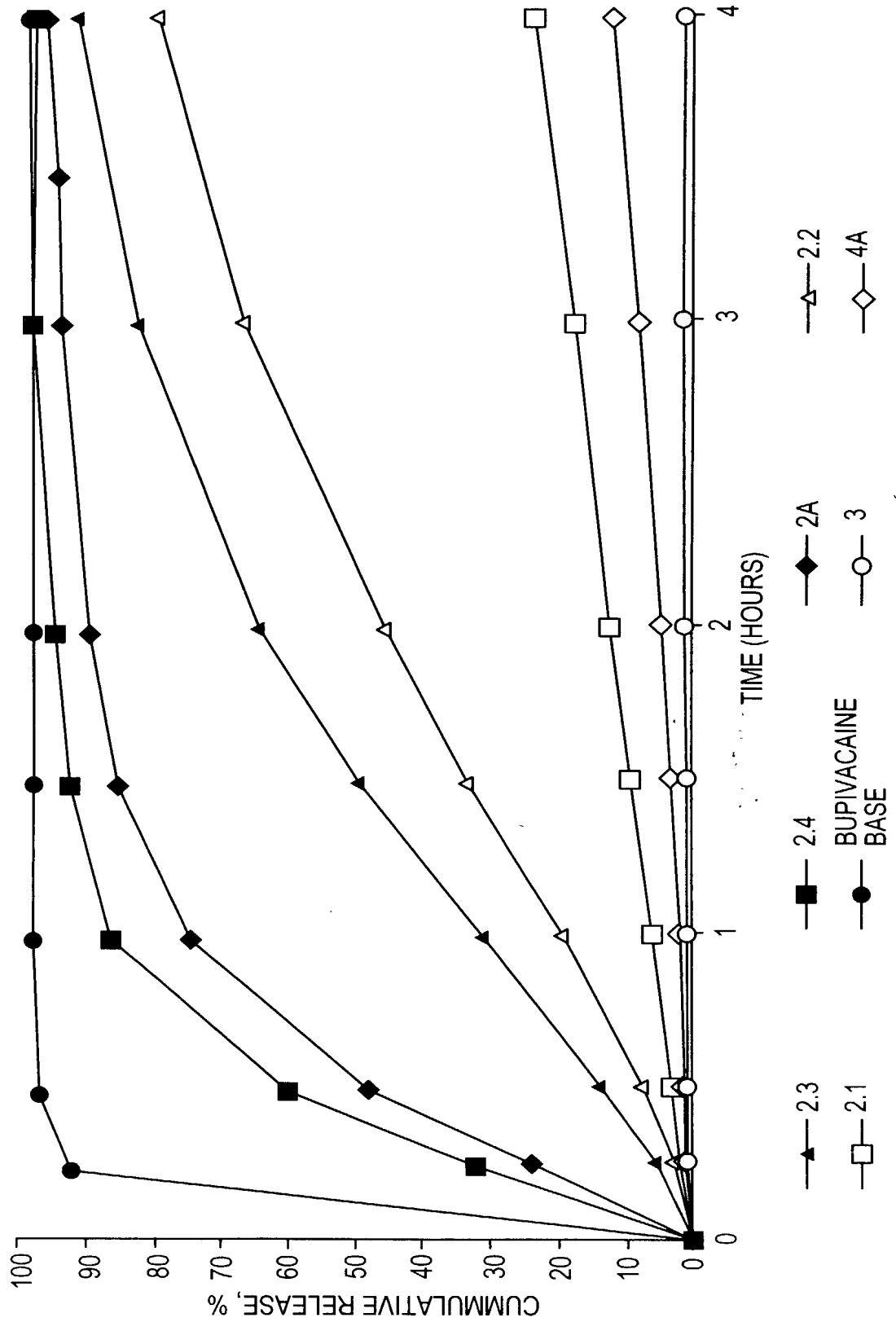


FIG. 1

IN VITRO RELEASE, pH 3.0, 37° C, PADDLE



2 / 57

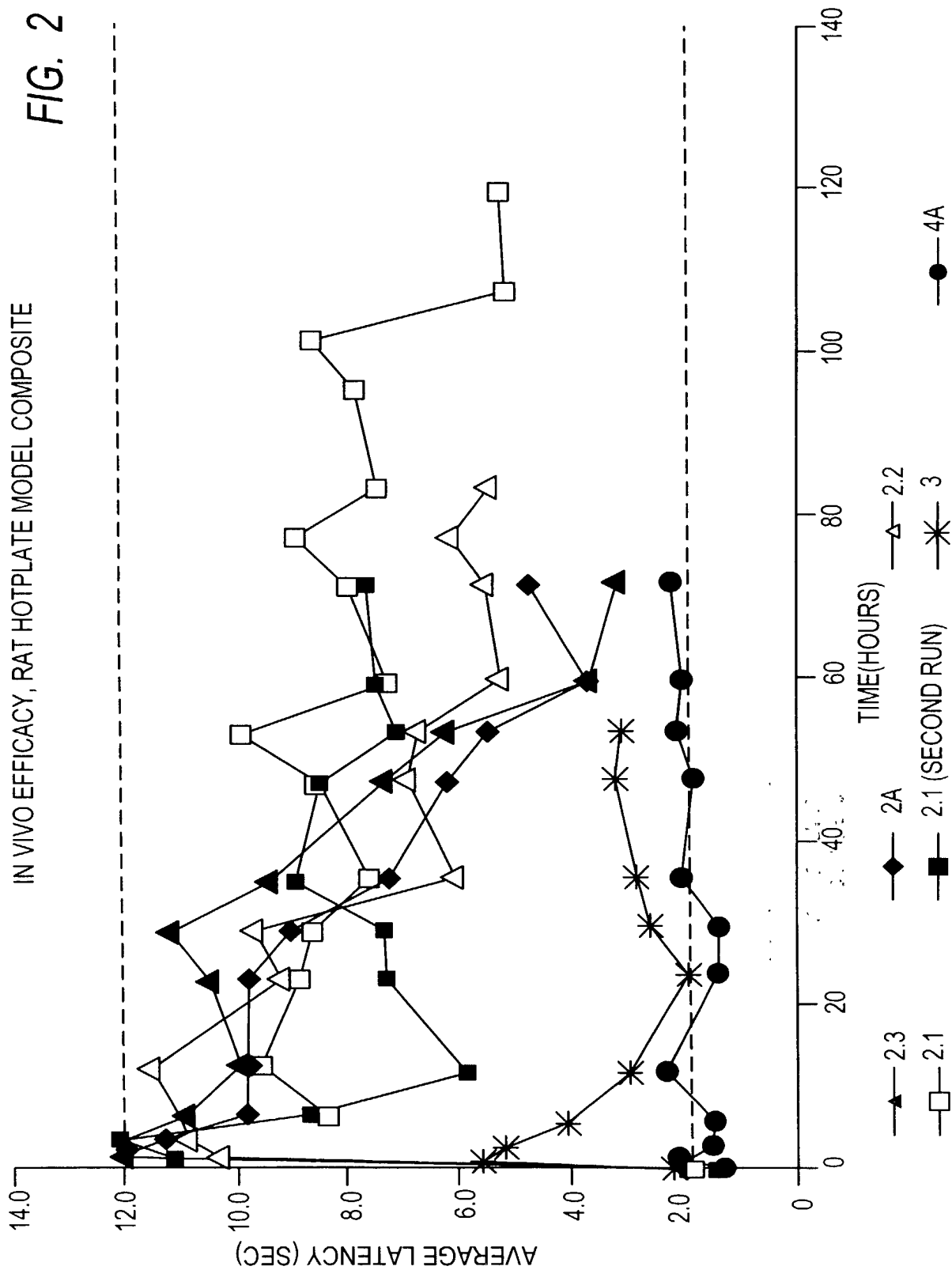
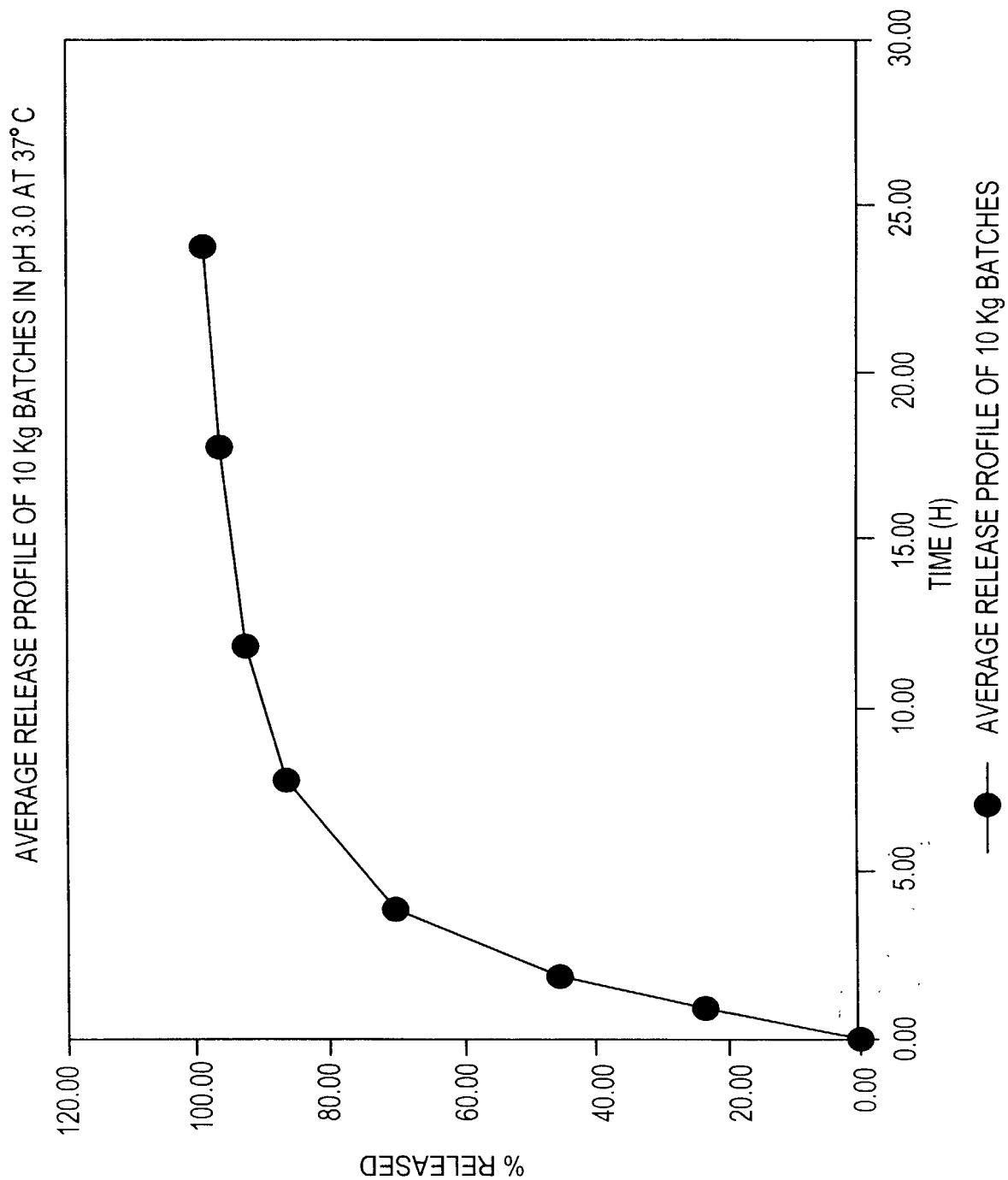


FIG. 3



MEAN LEVEL OVER TIME OF MEDIAN MECHANICAL PAIN DETECTION THRESHOLD (MPDT) PART I

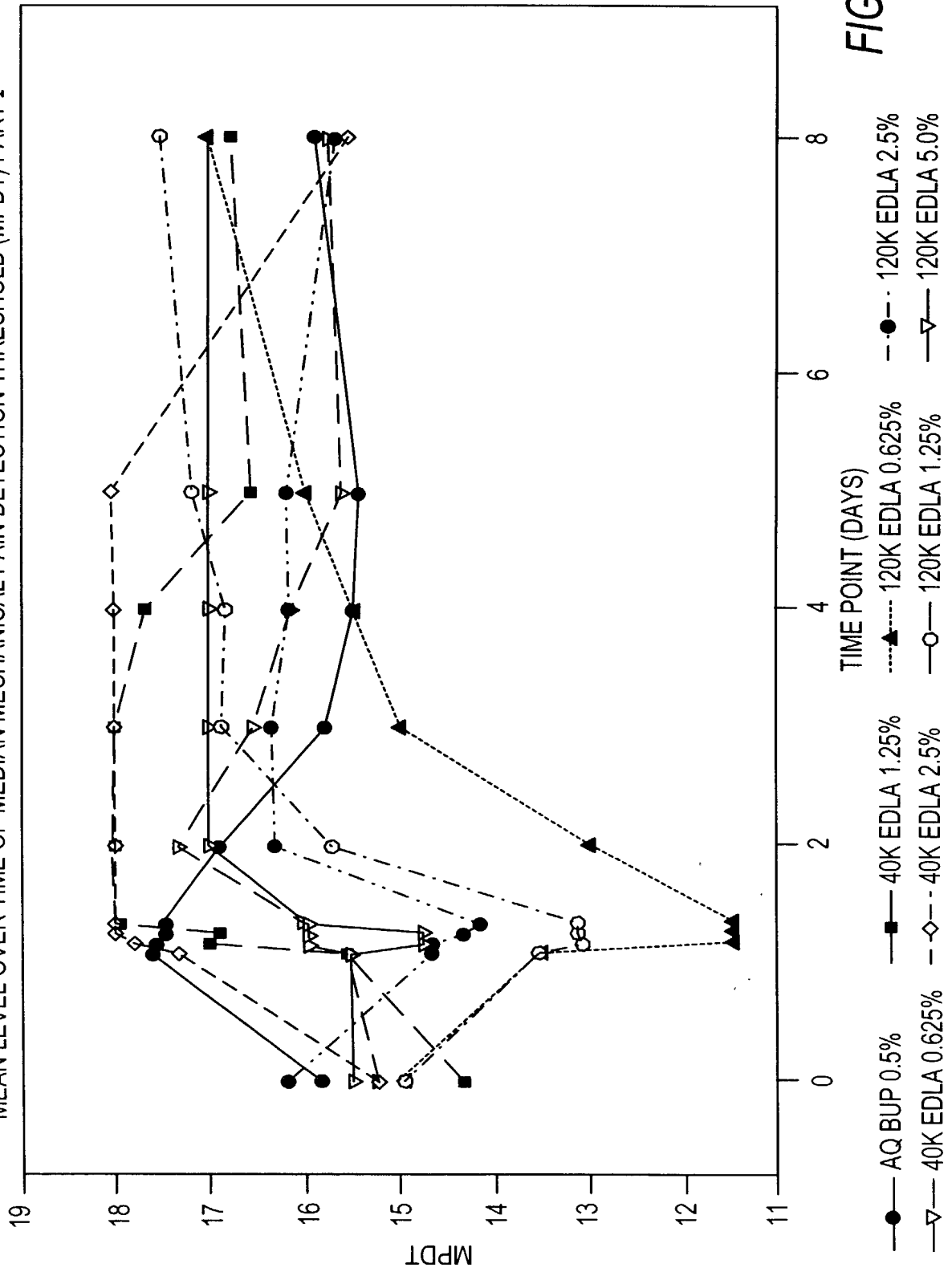


FIG. A1

MEAN LEVEL OVER TIME OF MEDIAN MECHANICAL PAIN DETECTION THRESHOLD (MPDT)
PART II - BILATERAL INJECTION OF 40K EDLA AND 40K IDLA (ONE PER CALF)

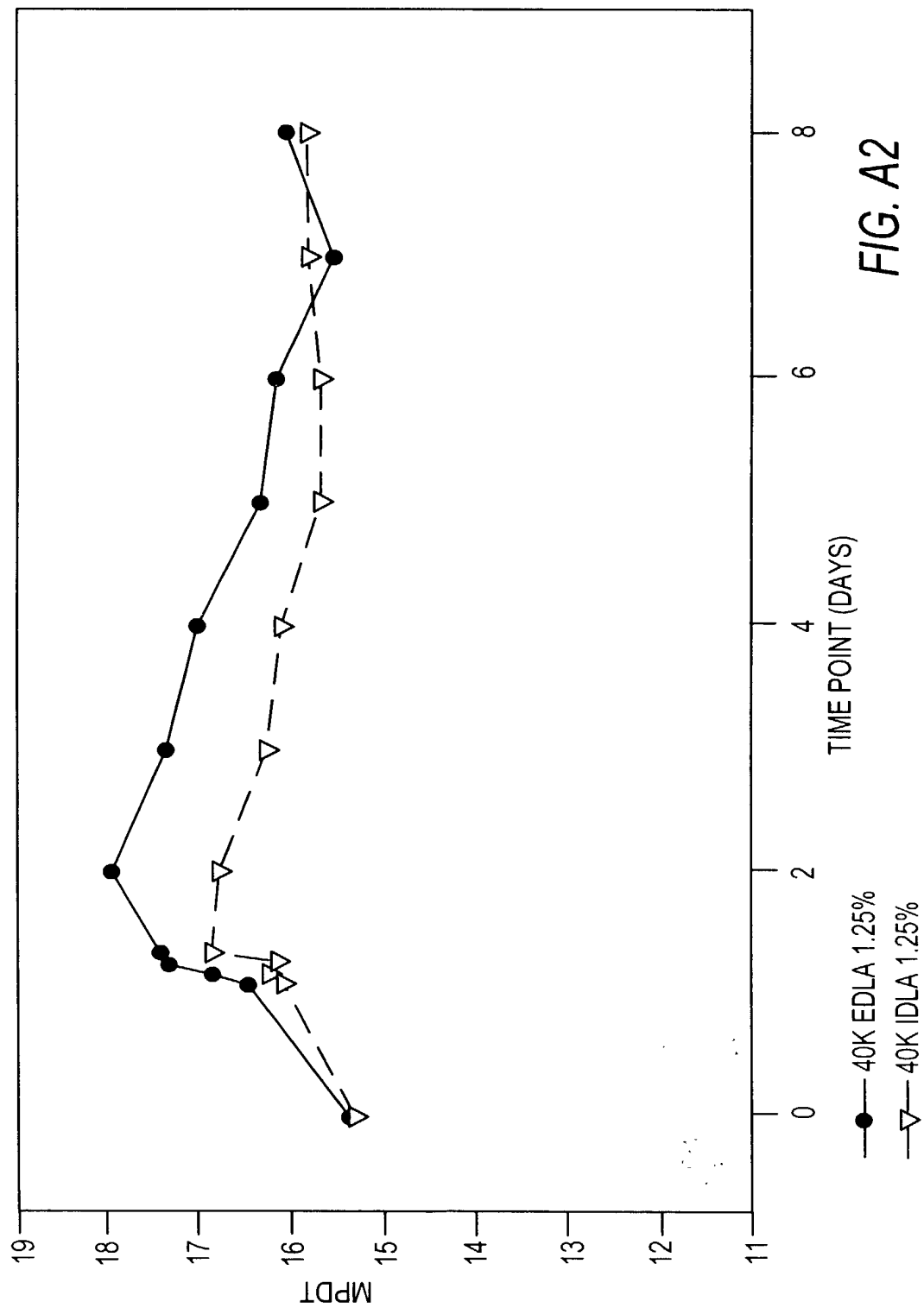


FIG. A2

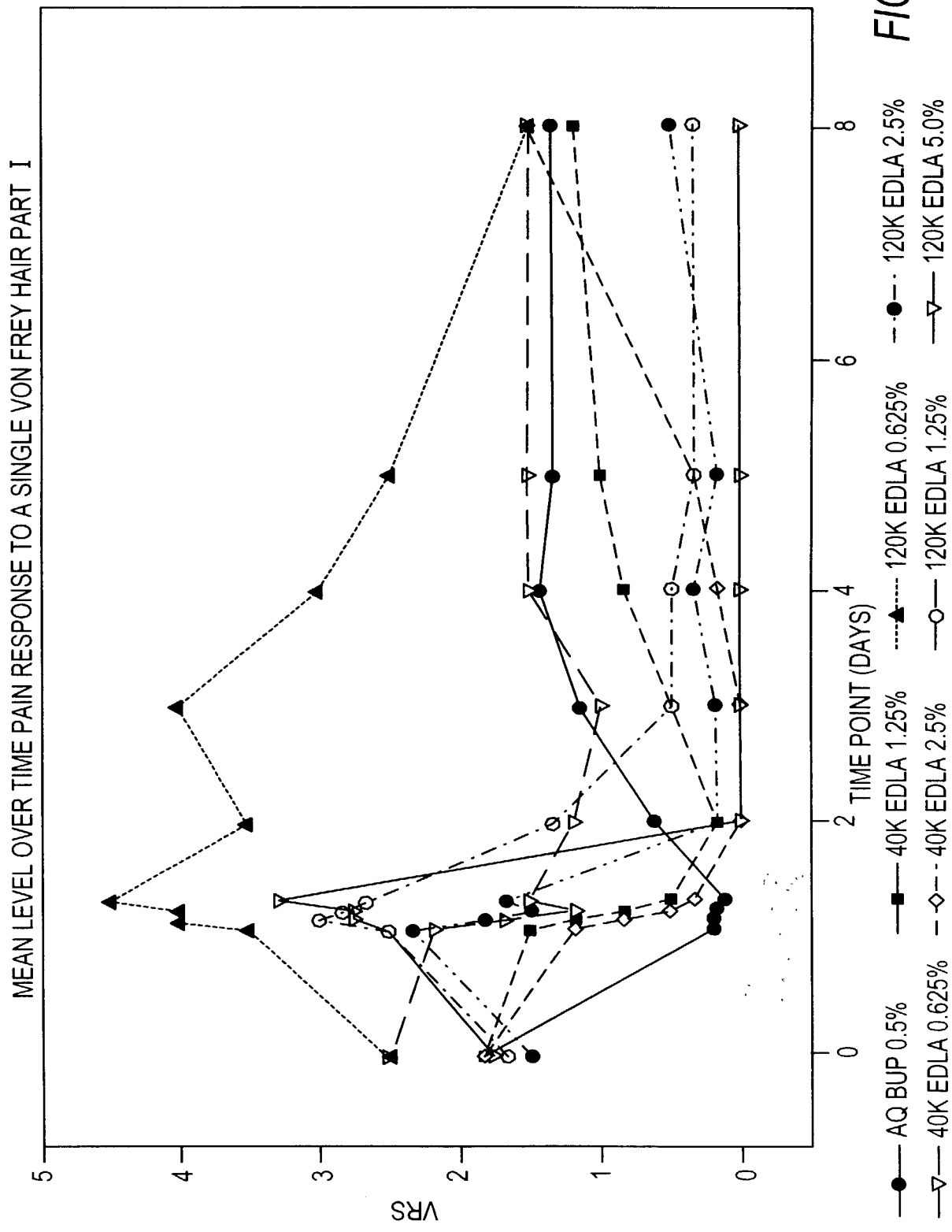
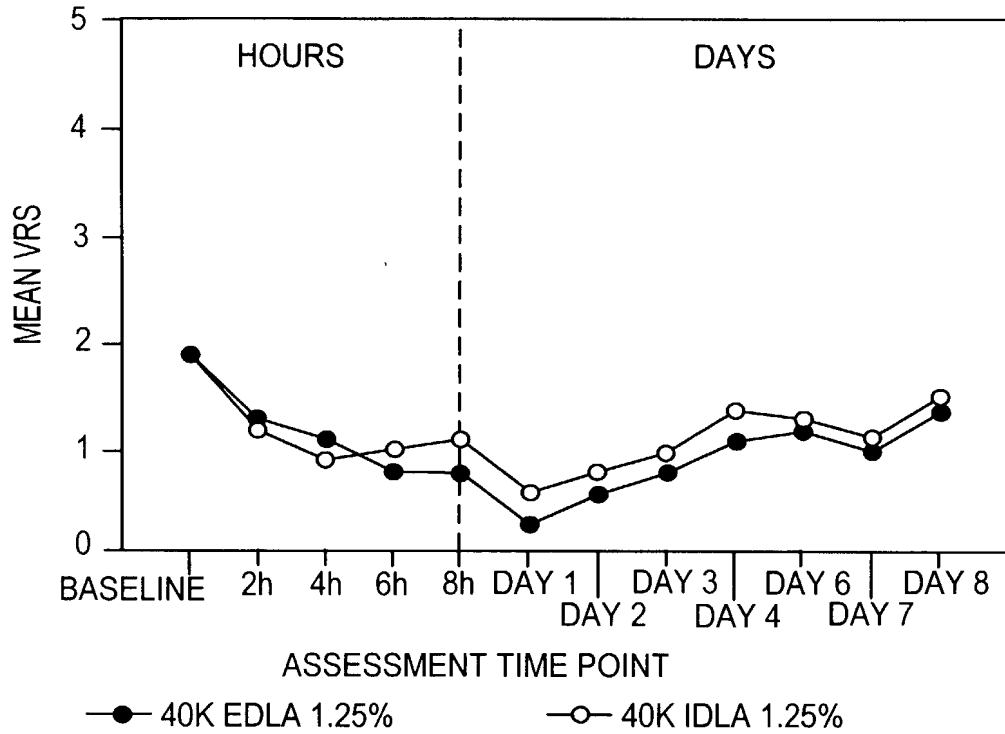


FIG. A3

7 / 57



| | BASE-LINE | h2 | h4 | h6 | h8 | h24 | DAY 2 | DAY 3 | DAY 4 | DAY 6 | DAY 7 | DAY 8 |
|------------------------|-----------|-----|-----|-----|-----|-----|-------|-------|-------|-------|-------|-------|
| 40K EDLA 1.25% N=13 | | | | | | | | | | | | |
| VRS | | | | | | | | | | | | |
| MEAN | 1.9 | 1.3 | 1.1 | 0.8 | 0.8 | 0.3 | 0.6 | 0.8 | 1.1 | 1.2 | 1.0 | 1.4 |
| (SE) | .3 | 0.2 | 0.2 | 0.2 | 0.3 | 0.1 | 0.4 | 0.5 | 0.7 | 0.6 | 0.6 | 0.6 |
| MEDIAN | 2 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| RANGE | 1,4 | 0,2 | 0,2 | 0,2 | 0,3 | 0,1 | 0,5 | 0,6 | 0,8 | 0,7 | 0,7 | 0,8 |
| 40K IDLA 1.25% N=13 | | | | | | | | | | | | |
| VRS | | | | | | | | | | | | |
| MEAN | 1.9 | 1.2 | 0.9 | 1.0 | 1.1 | 0.6 | 0.8 | 1 | 1.4 | 1.3 | 1.1 | 1.5 |
| (SE) | 0.3 | 0.2 | 0.2 | 0.2 | 0.3 | 0.2 | 0.3 | 0.3 | 0.7 | 0.6 | 0.6 | 0.7 |
| MEDIAN | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| RANGE | 1,4 | 0,3 | 0,2 | 0,2 | 0,3 | 0,2 | 0,3 | 0,4 | 0,9 | 0,8 | 0,8 | 0,9 |

FIG. A4

8/57

MEAN LEVEL OVER TIME OF MEDIAN MECHANICAL TOUCH DETECTION THRESHOLD (MTDT) PART I

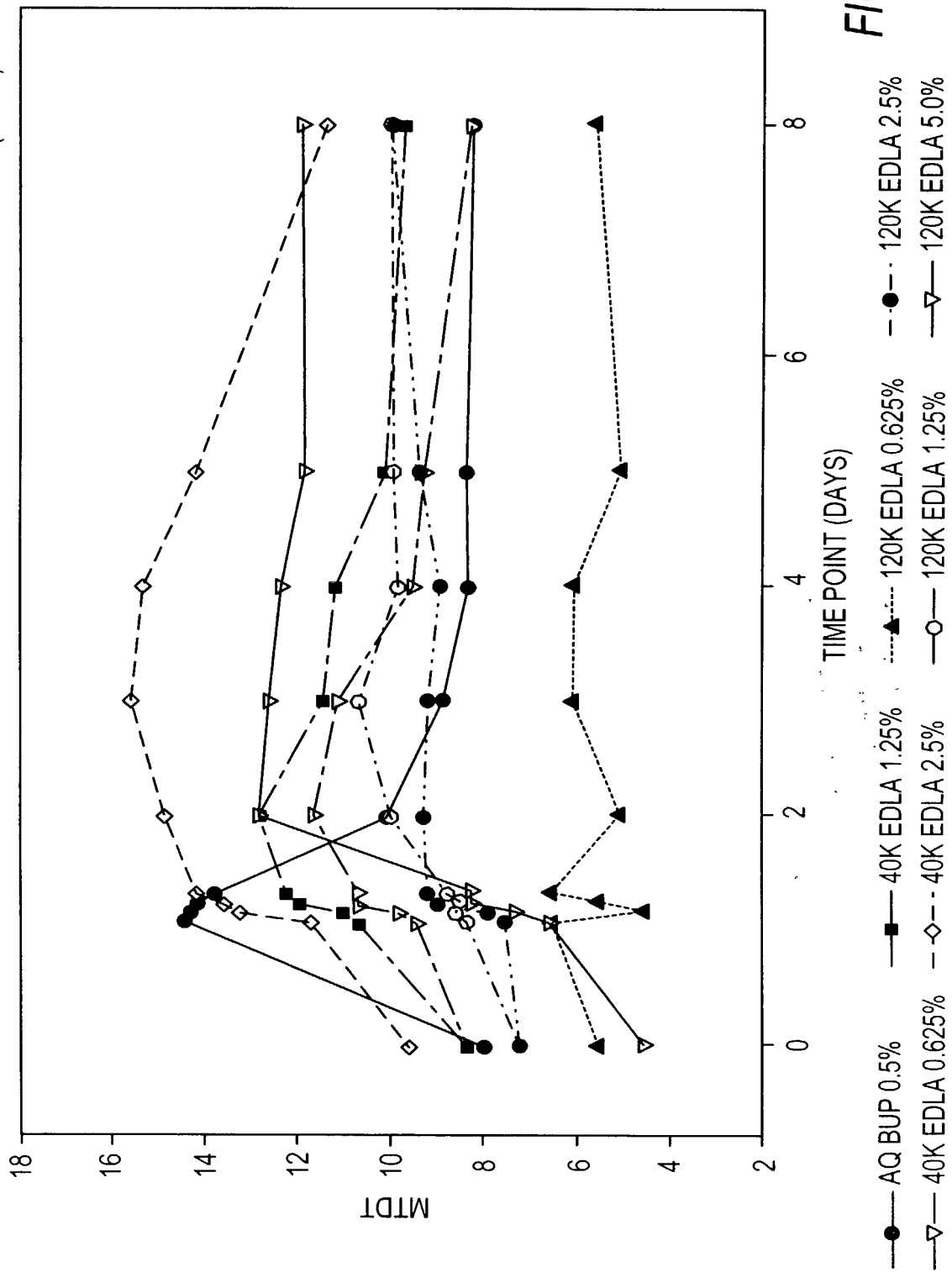


FIG. A5



MEAN LEVEL OVER TIME OF SUPRATHRESHOLD PAIN RESPONSE TO HEAT FOR STUDY PART I

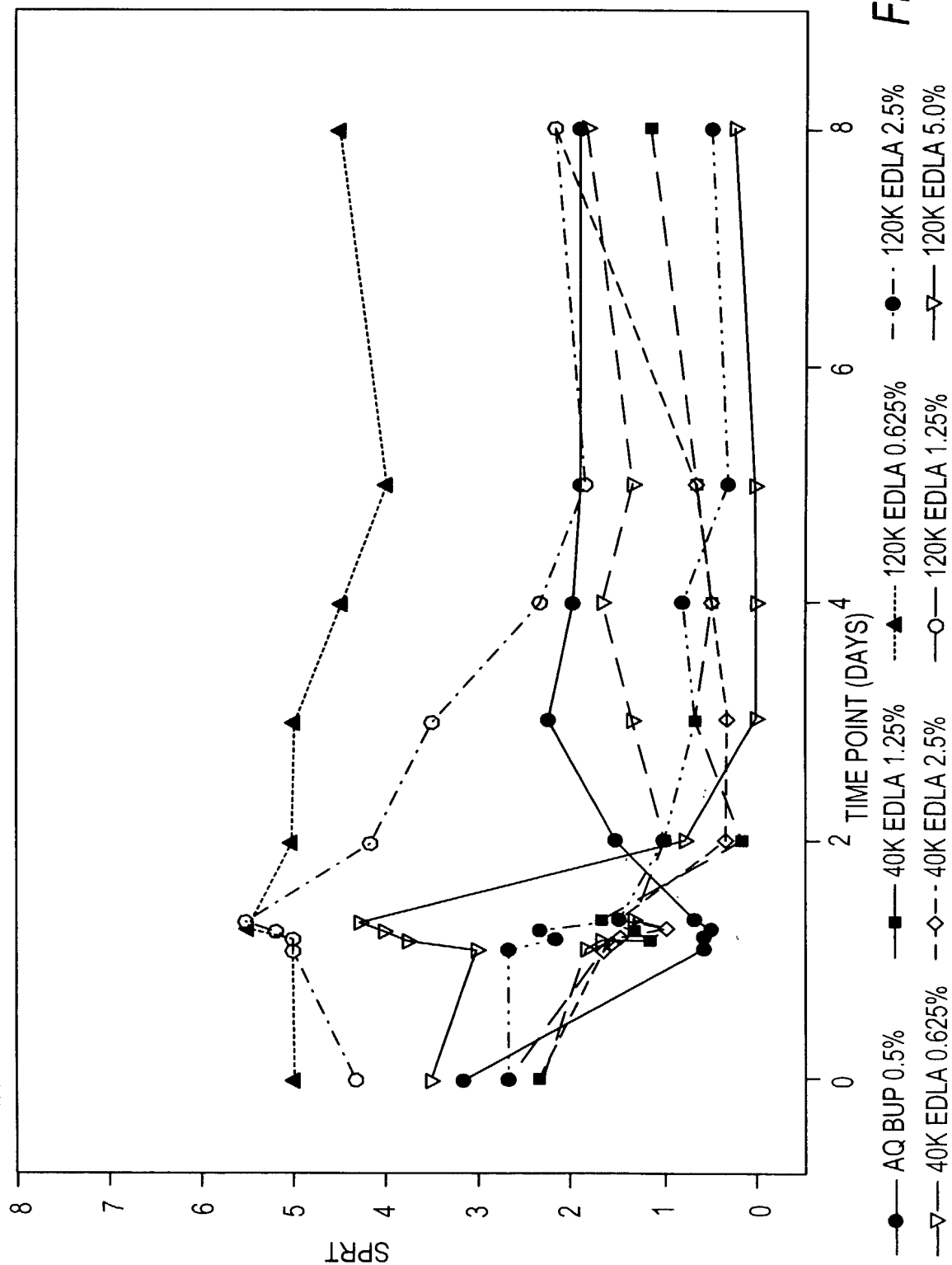


FIG. A7

MEAN LEVEL OVER TIME OF SUPRATHRESHOLD PAIN RESPONSE TO HEAT FOR STUDY
PART II - BILATERAL INJECTION OF 40K EDLA AND 40K IDLA (ONE PER CALF)

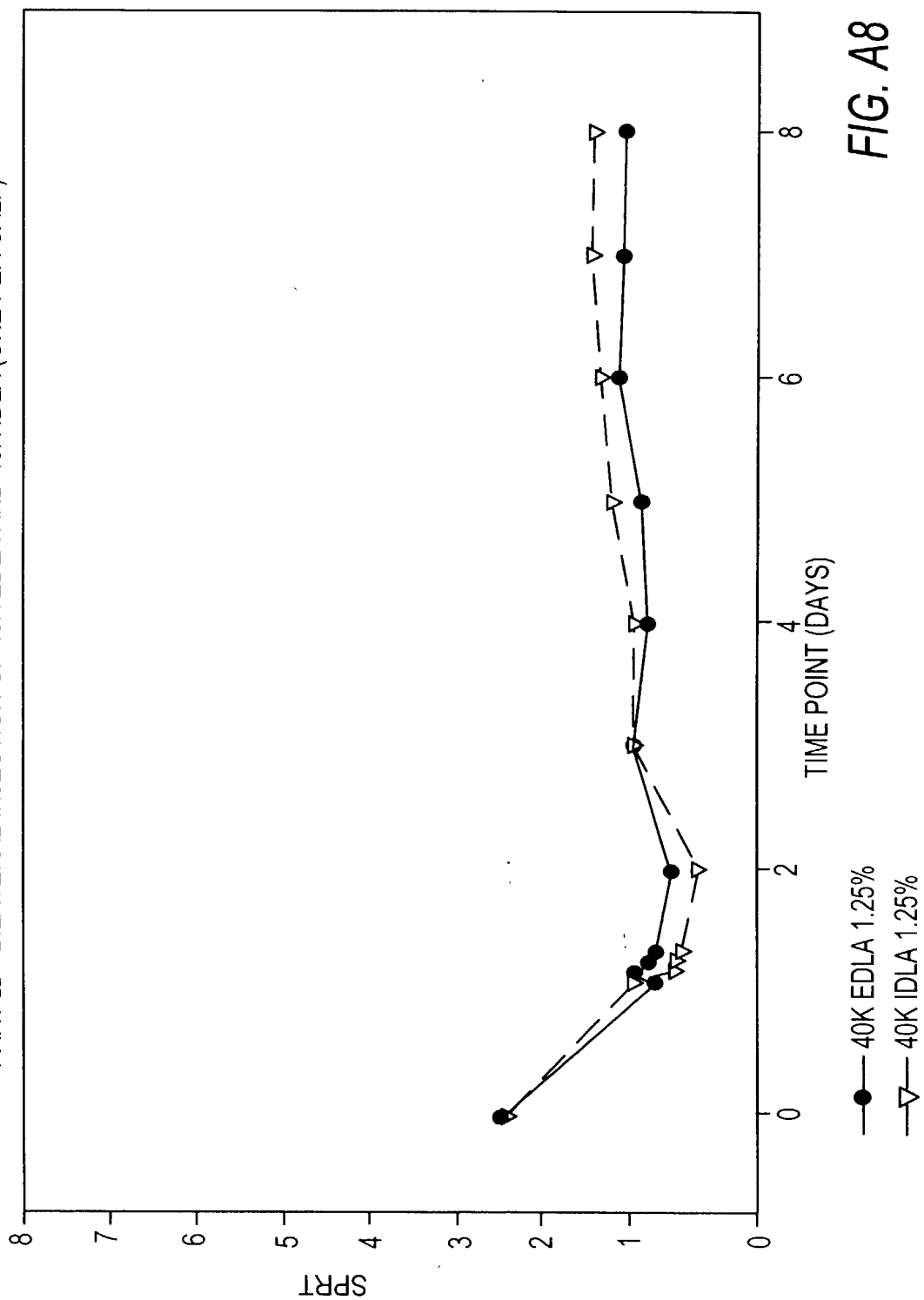


FIG. A8

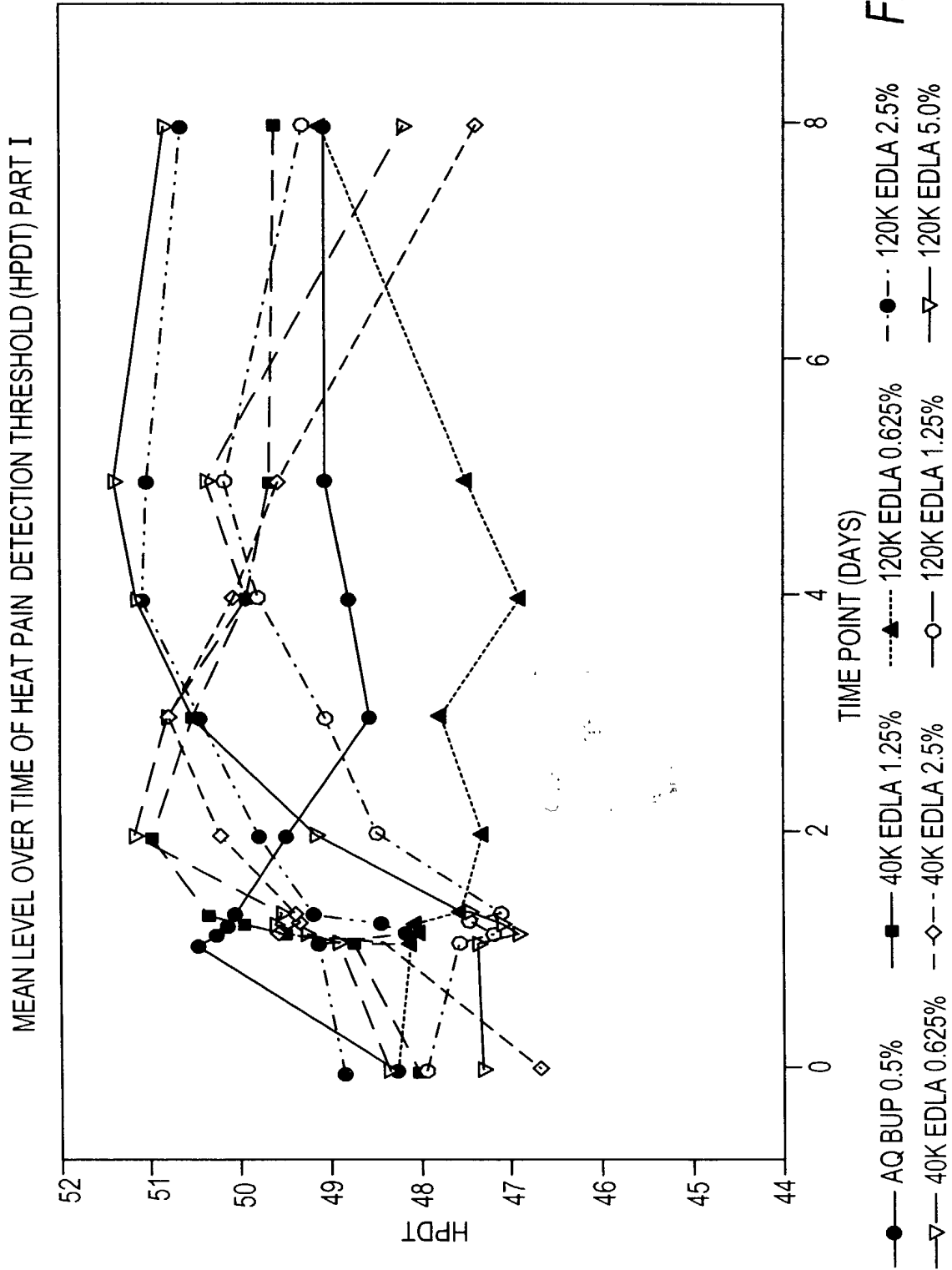


FIG. A9

MEAN LEVEL OVER TIME OF HEAT PAIN DETECTION THRESHOLD (HPDT)
PART II - BILATERAL INJECTION 40K EDLA AND 40K IDLA (ONE PER CALF)

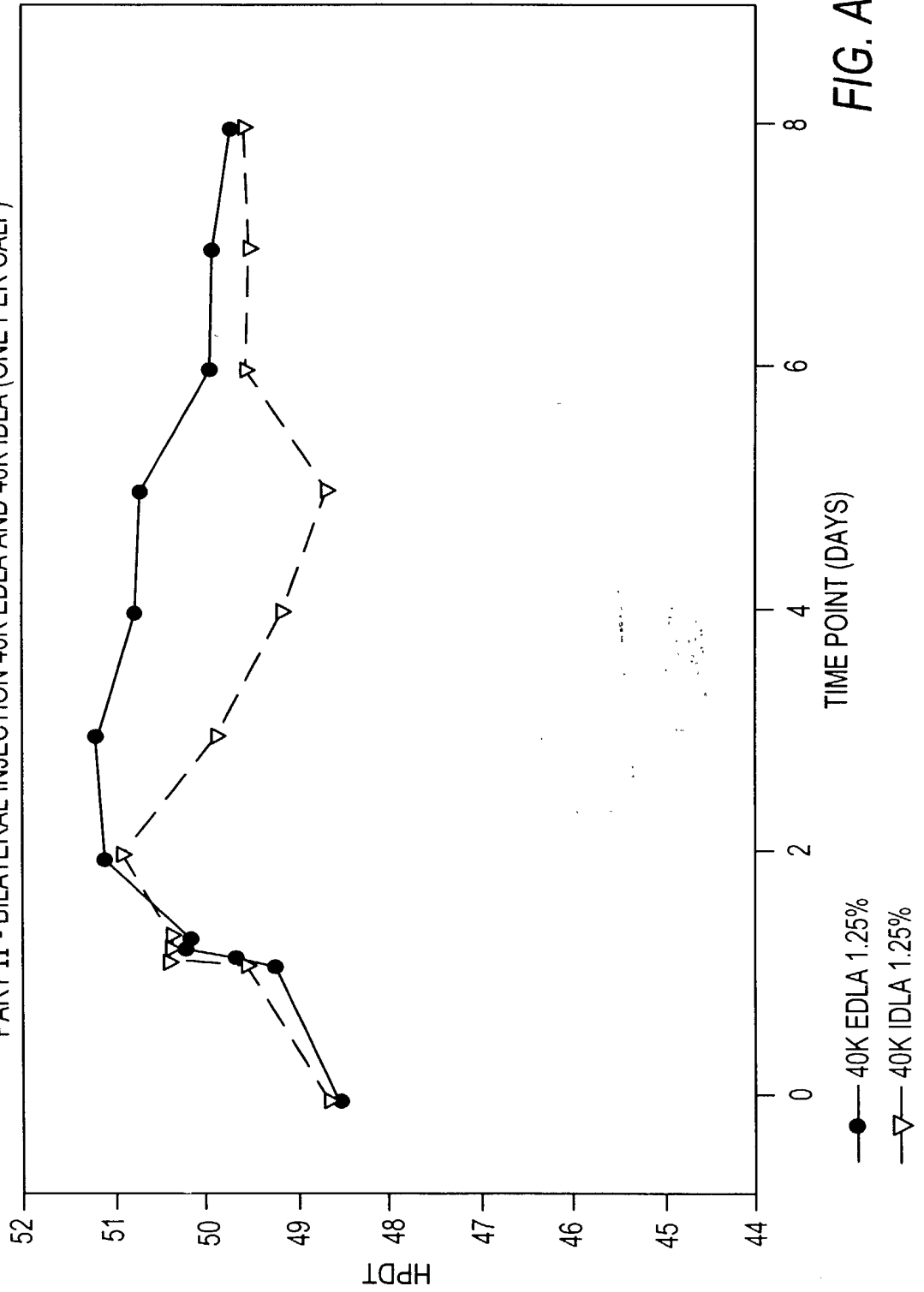


FIG. A10

MEAN LEVEL OVER TIME OF MEDIAN WARM DETECTION THRESHOLD (WDT) PART I

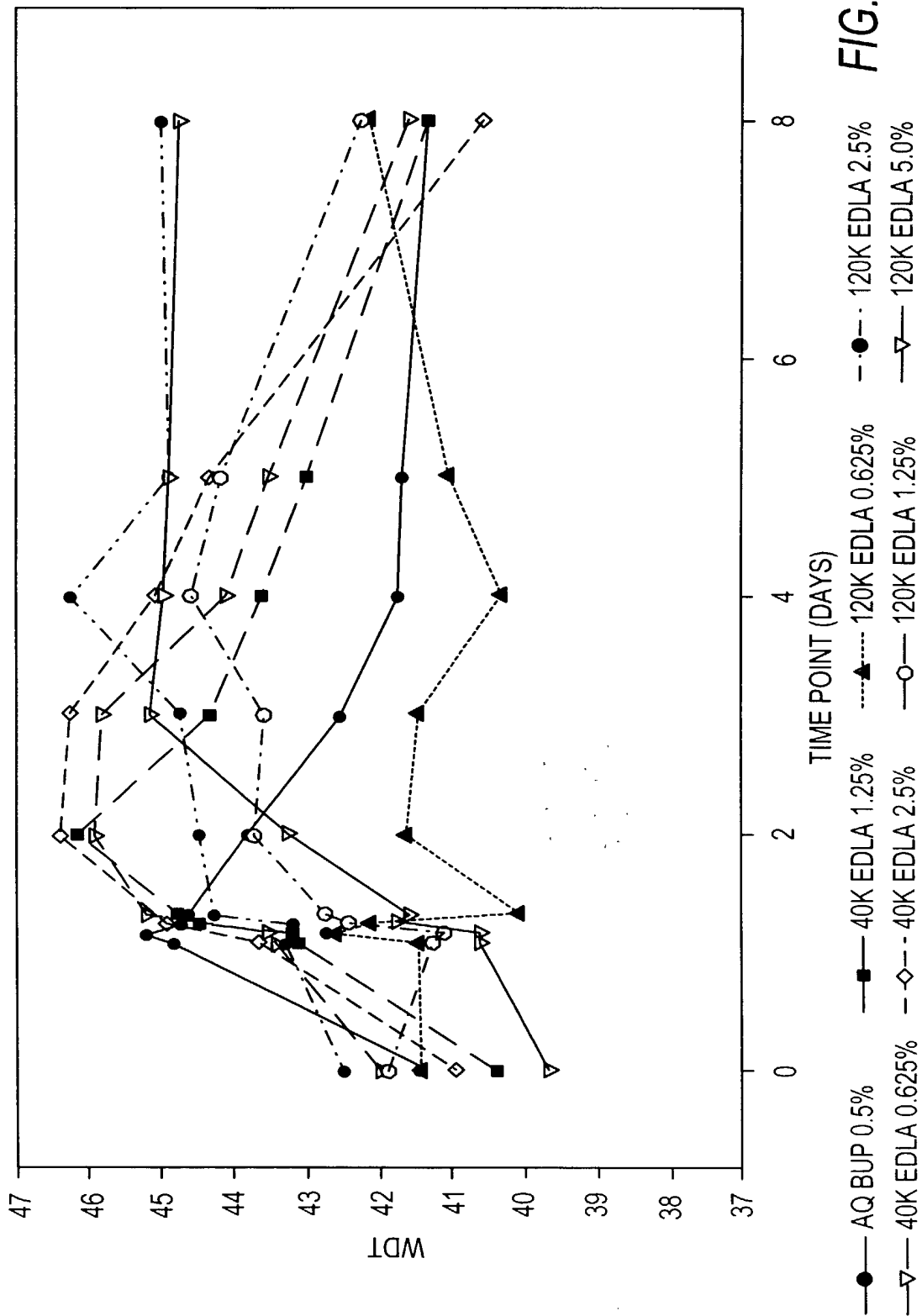


FIG. A11

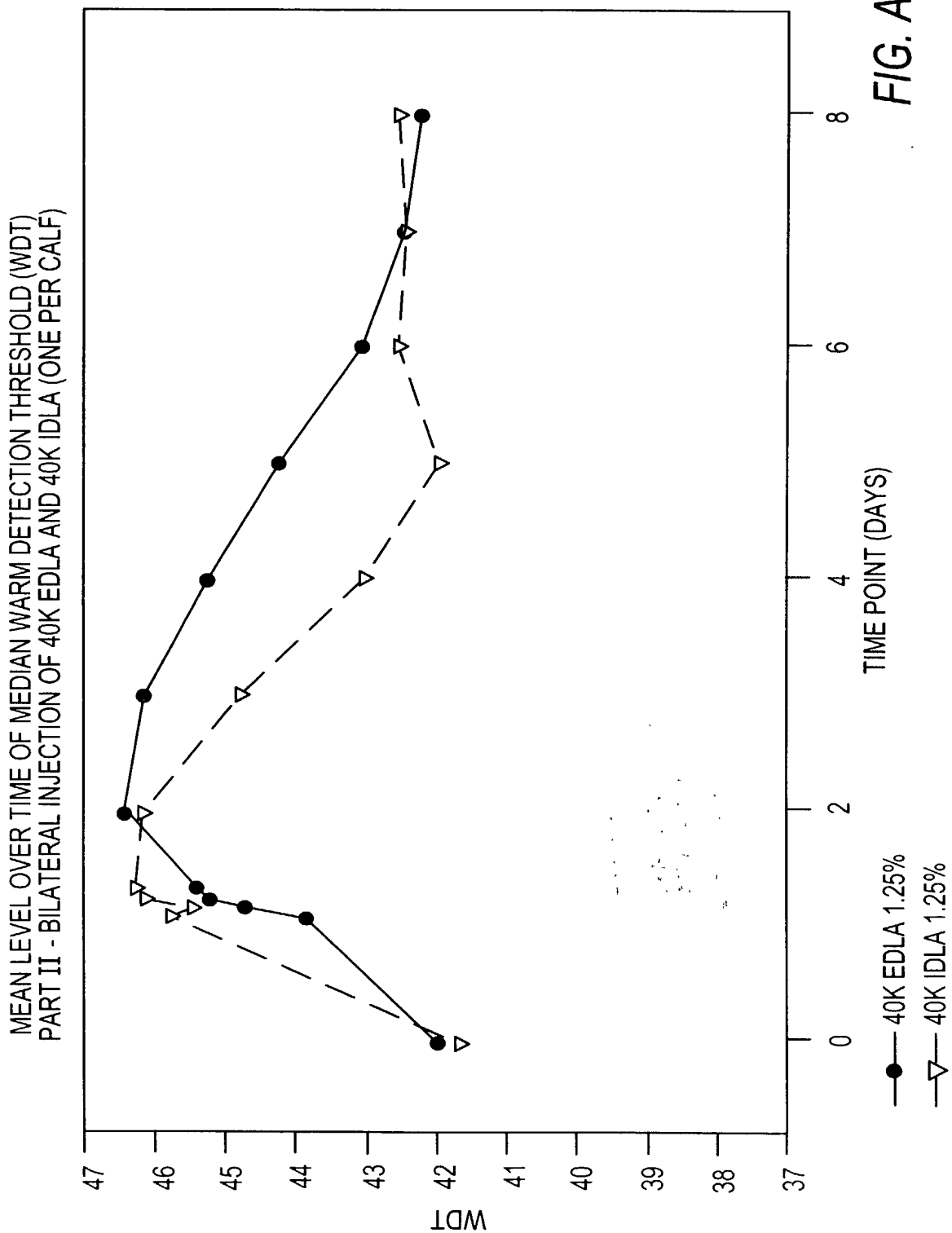


FIG. A12

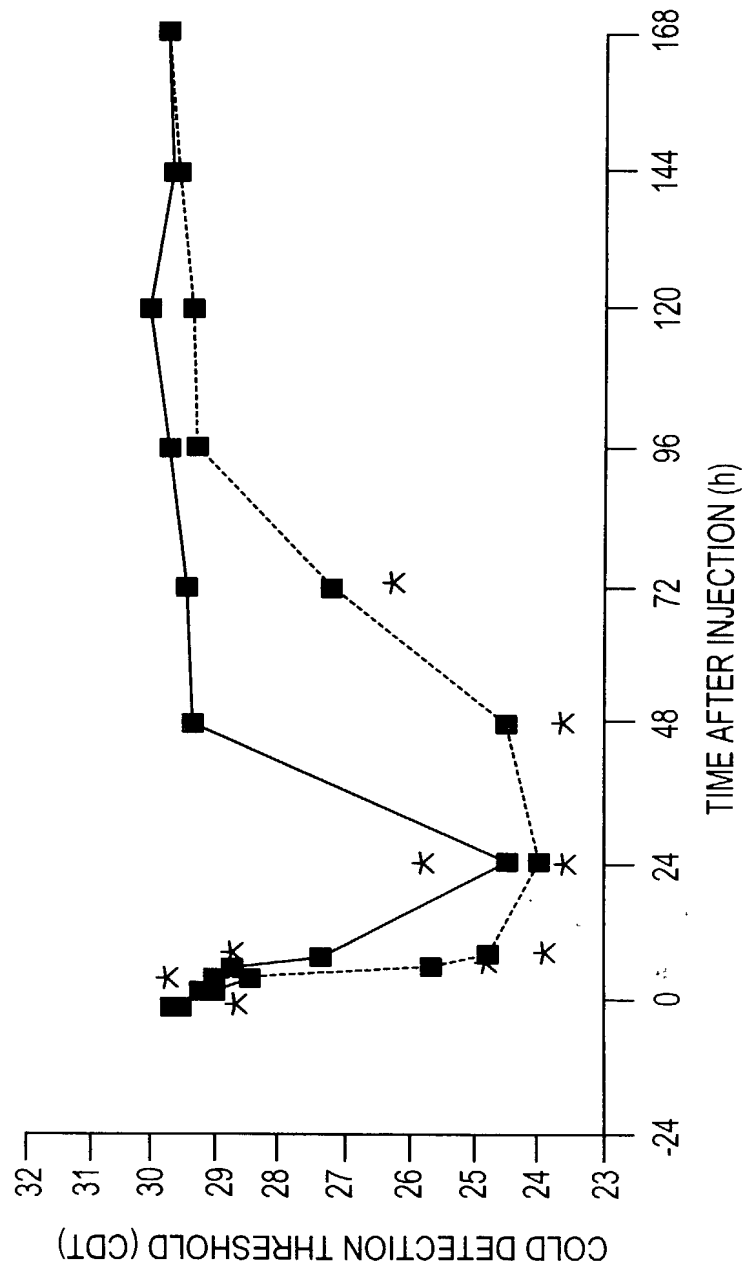


FIG. A13

MEAN LEVEL OF ANALGESIA/ANESTHESIA (PIN - PRICK TEST) OVER TIME BY TREATMENT

POPULATION : ALL SUBJECTS ENROLLED IN STUDY

STUDY PHASE 1 = FORMULA = 120K

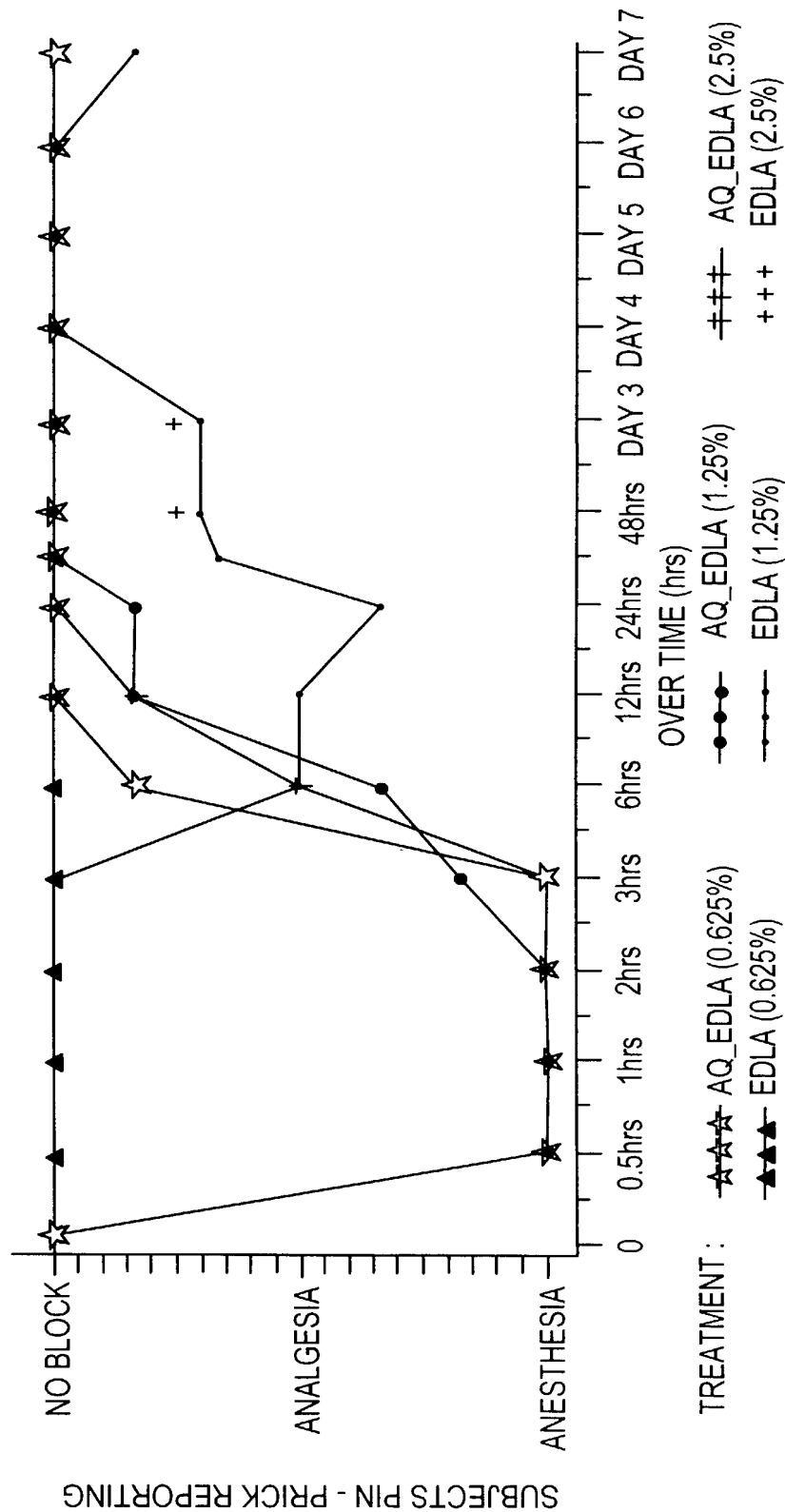


FIG. C1

MEAN LEVEL OF ANALGESIA/ANESTHESIA (PIN - PRICK TEST) OVER TIME BY TREATMENT
 POPULATION : ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE 1 = FORMULA = 40K

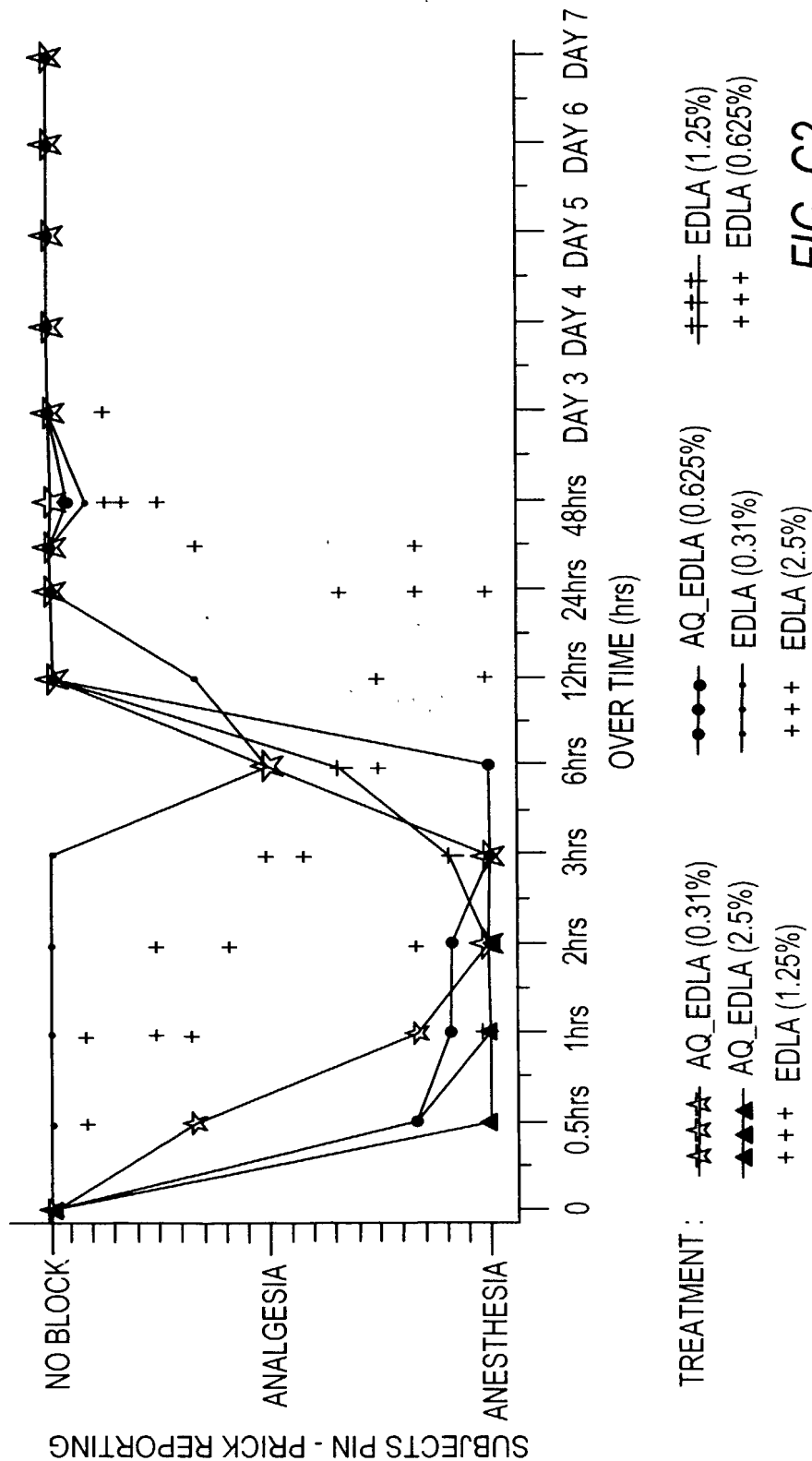


FIG. C2

MEAN LEVEL OF ANALGESIA/ANESTHESIA (PIN - PRICK TEST) OVER TIME BY TREATMENT
POPULATION : ALL SUBJECTS ENROLLED IN STUDY
STUDY PHASE = 2 FORMULA = 40K

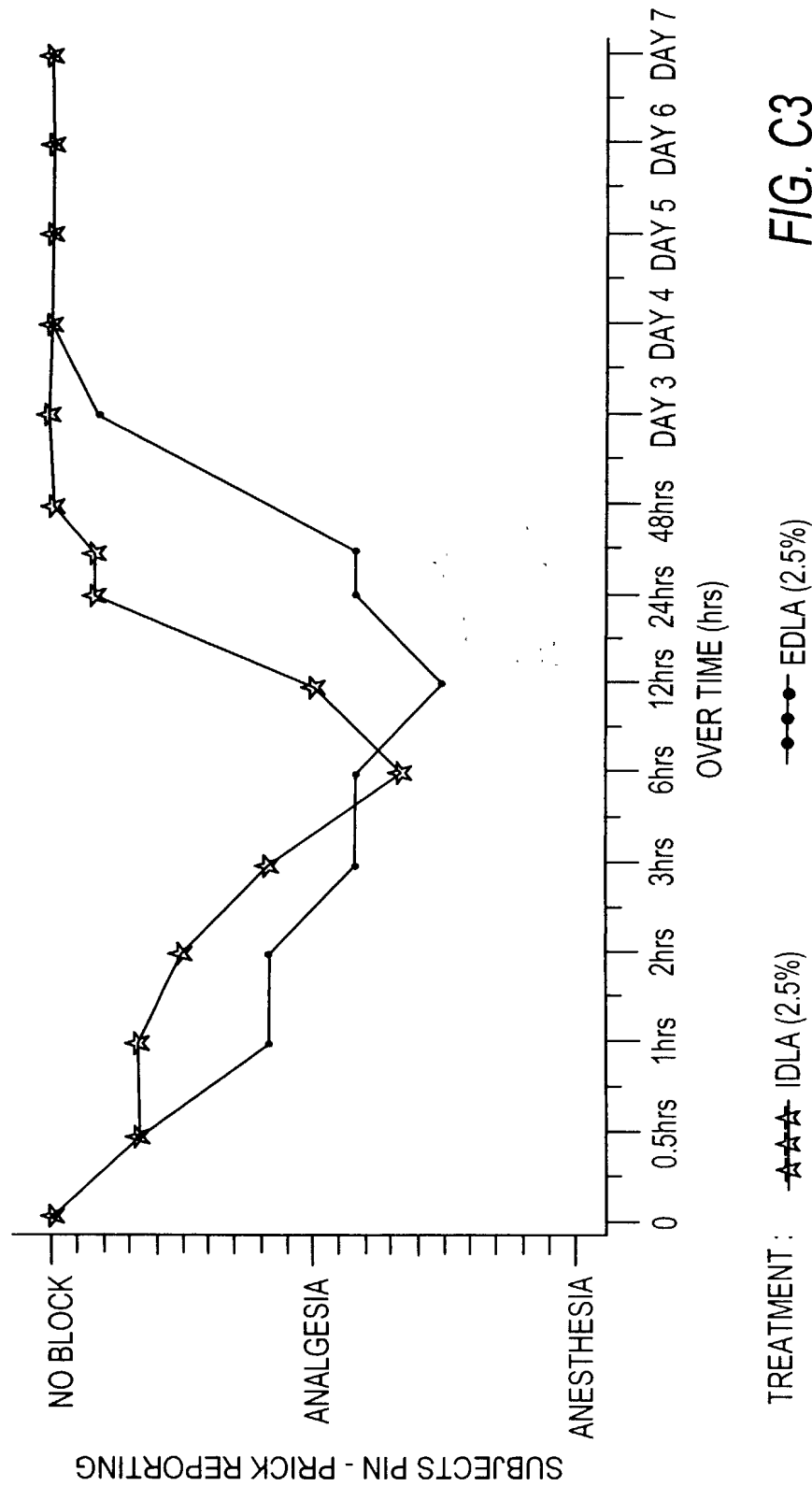
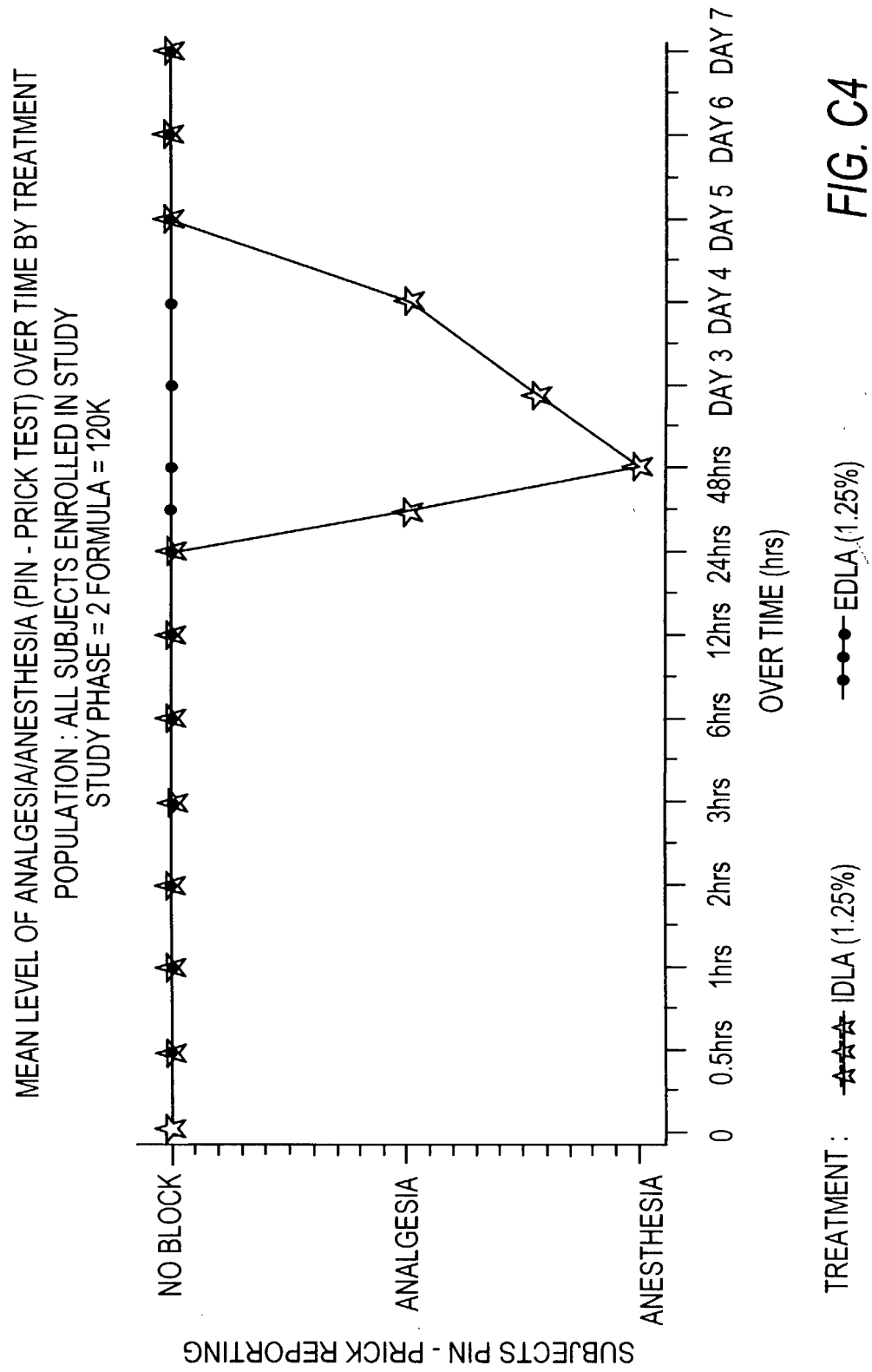
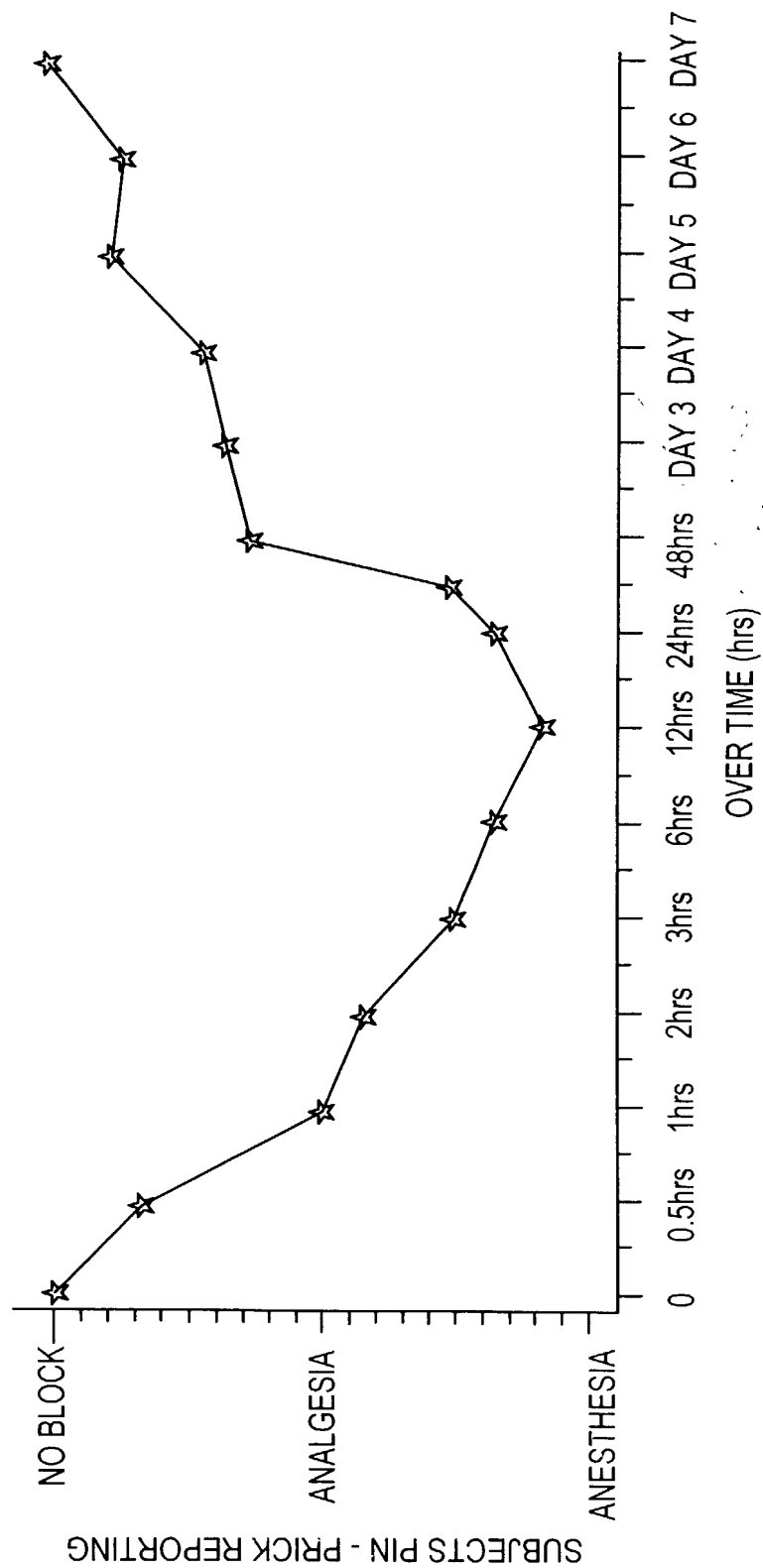


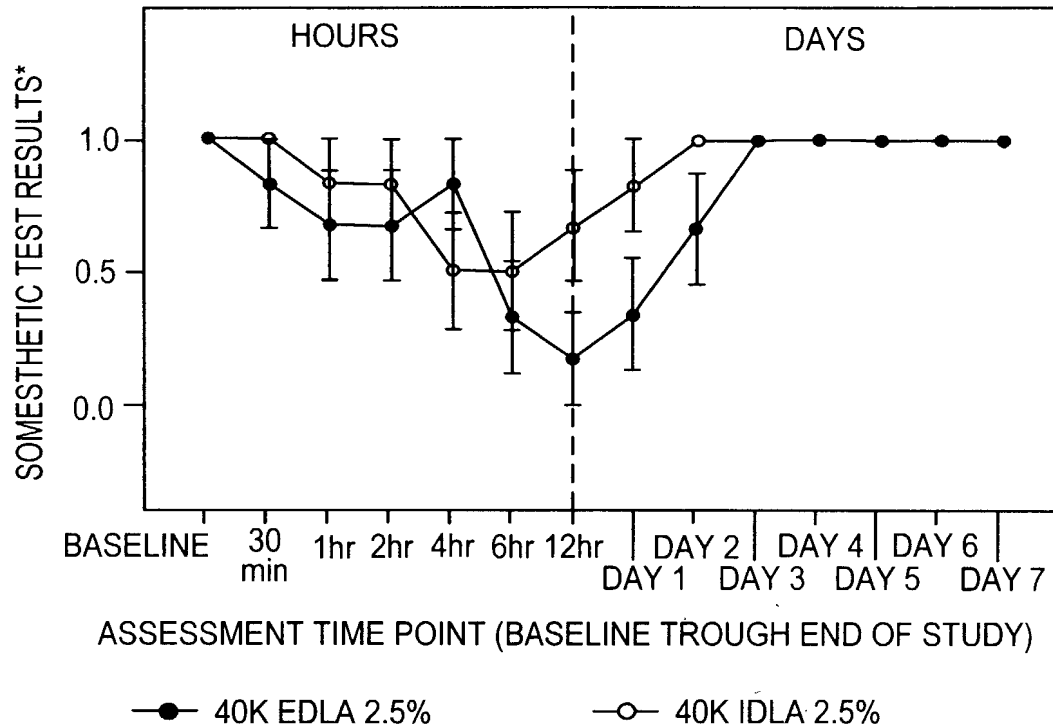
FIG. C3



MEAN LEVEL OF ANALGESIA/ANESTHESIA (PIN - PRICK TEST) OVER TIME BY TREATMENT
 POPULATION : ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 3 FORMULA = 40K



TREATMENT : ~~---~~ EDLA (5.0%) **FIG. C5**



| BASE -LINE | 30 min | Hr 1 | Hr 2 | Hr 3 | Hr 6 | Hr 12 | DAY 1 | DAY 2 | DAY 3 | DAY 4 | DAY 5 | DAY 6 | DAY 6 |
|----------------------|-----------|---------|---------|---------|---------|----------|----------|----------|----------|----------|----------|----------|----------|
| 40K EDLA 2.5% N=6 | | | | | | | | | | | | | |

SOMESTHETIC TEST RESULTS^a

| | | | | | | | | | | | | | | |
|---------|-----|-------|-------|-------|-------|-------|-------|-------|-------|-----|-----|-----|-----|-----|
| MEAN | 1.0 | 0.8 | 0.7 | 0.7 | 0.8 | 0.3 | 0.2 | 0.3 | 0.7 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| (SE) | (0) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0) | (0) | (0) | (0) | (0) |
| MINIMUM | 1.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| MAXIMUM | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |

40K IDLA 2.5%
N=6

SOMESTHETIC TEST RESULTS^a

| | | | | | | | | | | | | | | |
|---------|-----|-----|-------|-------|-------|-------|-------|-------|-----|-----|-----|-----|-----|-----|
| MEAN | 1.0 | 1.0 | 0.8 | 0.8 | 0.5 | 0.5 | 0.7 | 0.8 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| (SE) | (0) | (0) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0) | (0) | (0) | (0) | (0) | (0) |
| MINIMUM | 1.0 | 1.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| MAXIMUM | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |

^aEVALUATED ON A SCALE OF 0-2, WITH 0 = NO FEELING;
1 = FEELS TOUCH/PRESSURE; 2 = FEELS SHARP.

FIG. C6

MEAN LEVEL OF NUMBNESS OVER TIME BY TREATMENT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 1 FORMULA = 120K

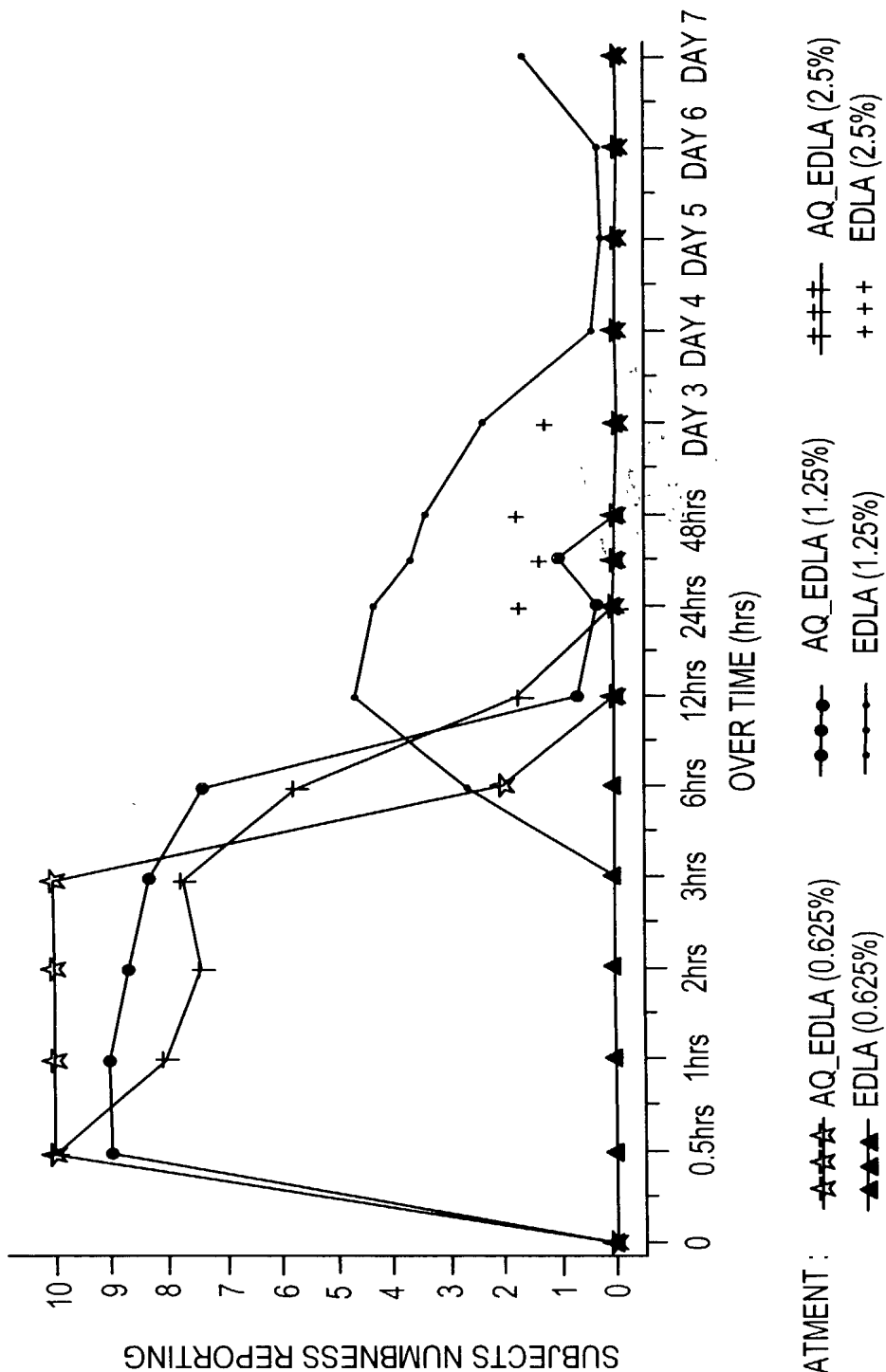


FIG. C7

MEAN LEVEL OF NUMBNESS OVER TIME BY TREATMENT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 1 FORMULA = 40K

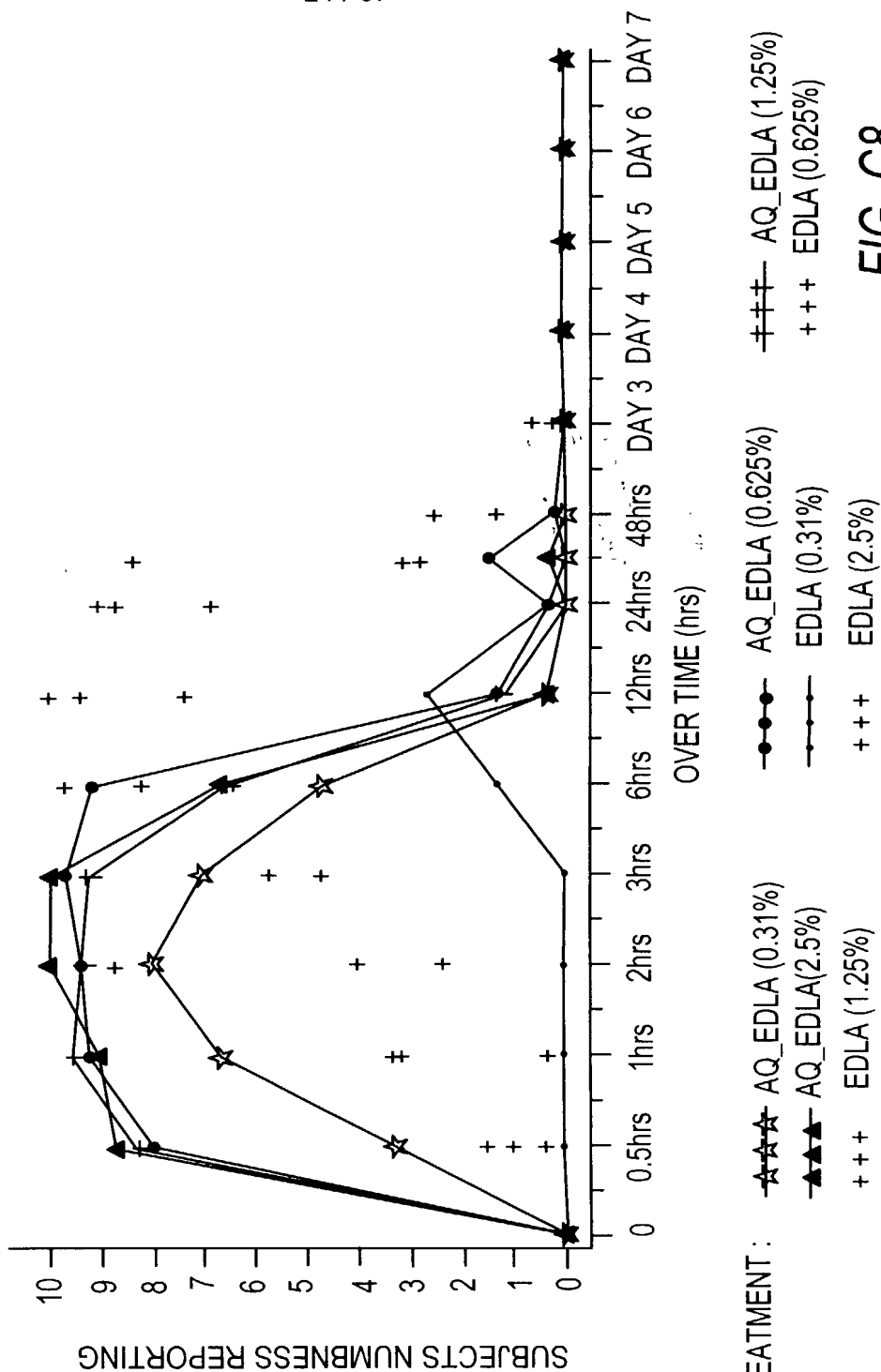


FIG. C8

MEAN PLASMA CONCENTRATION OF BUPIVACAINE (ng/ml) BY TIME POINT
POPULATION: ALL SUBJECTS ENROLLED IN STUDY
STUDY PHASE = 2 FORMULA = 40K

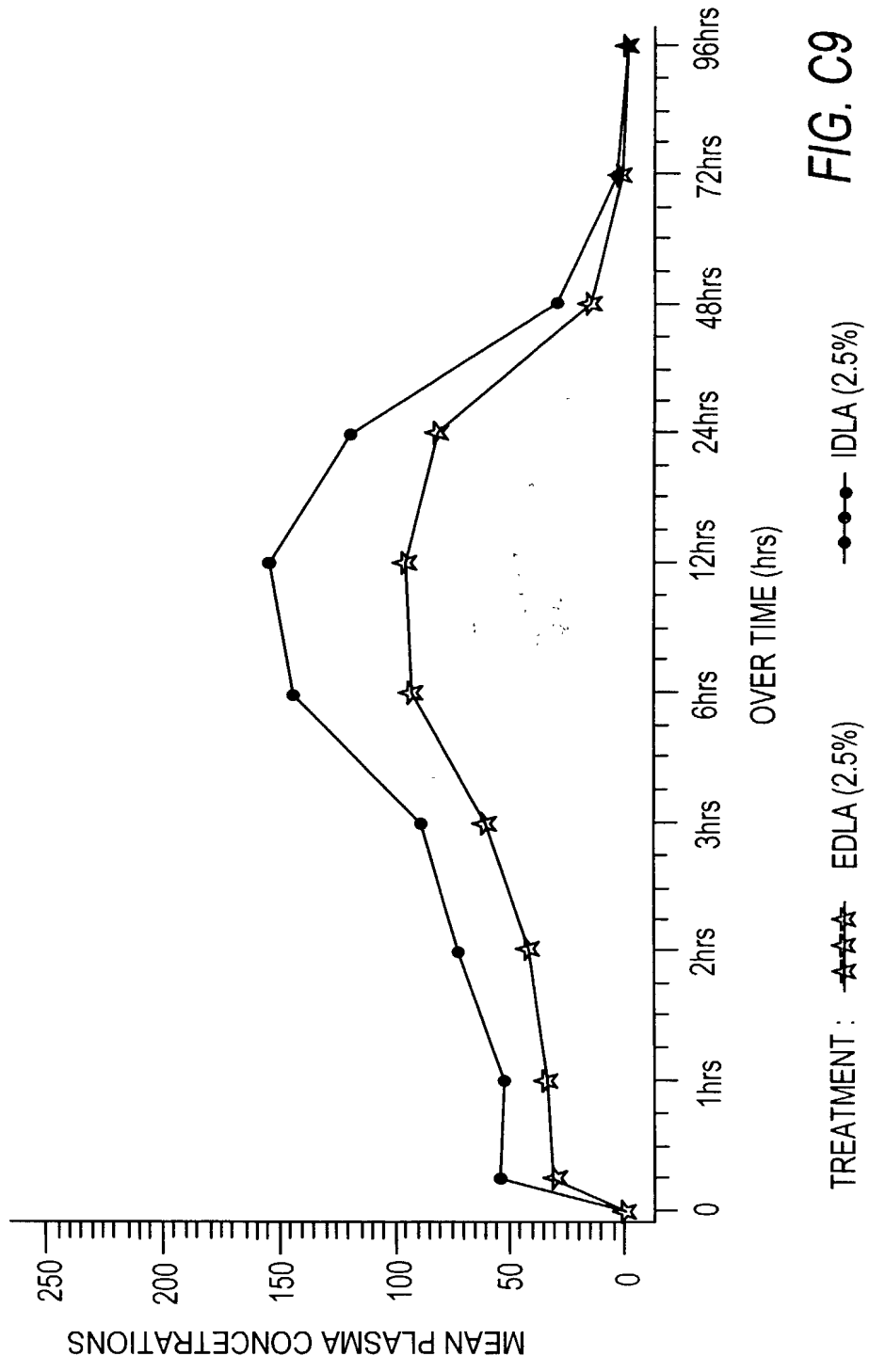
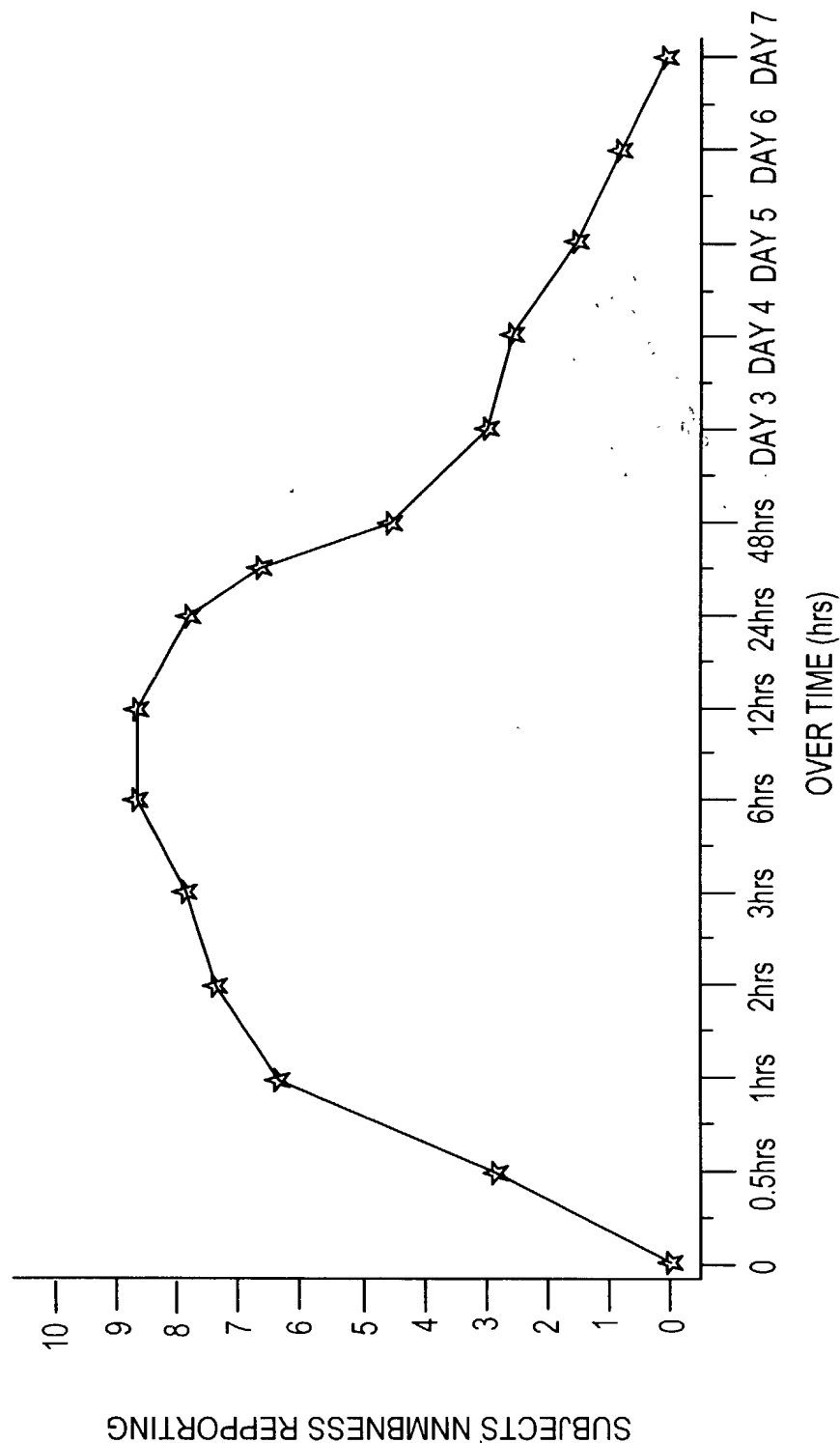


FIG. C9

MEAN LEVEL OF NUMBNESS OVER TIME BY TREATMENT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 3 FORMULA = 40K



TREATMENT : EDLA (5.0%)

FIG. C10

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 1 FORMULA = 120K

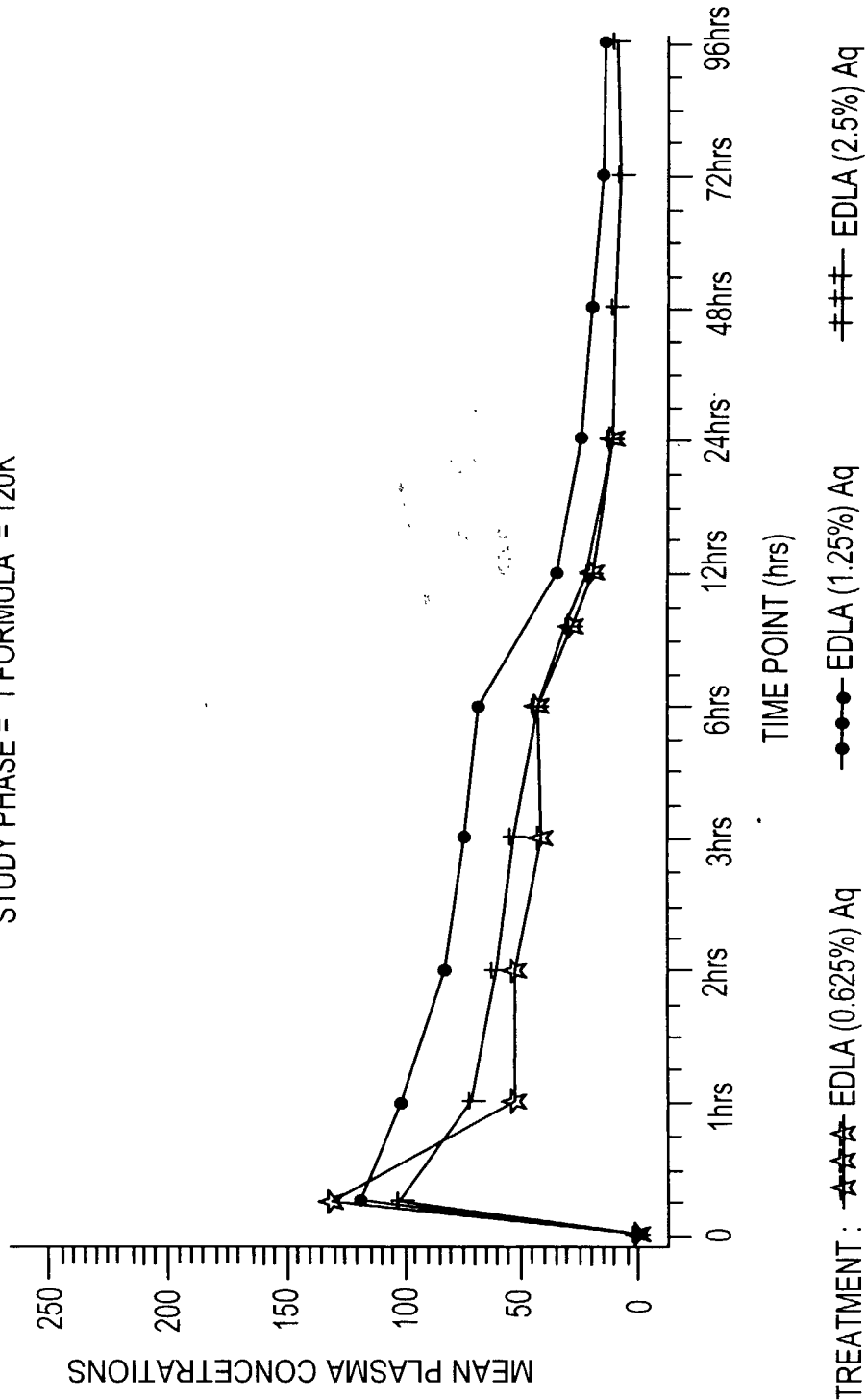


FIG. C11

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 1 FORMULA = 40K

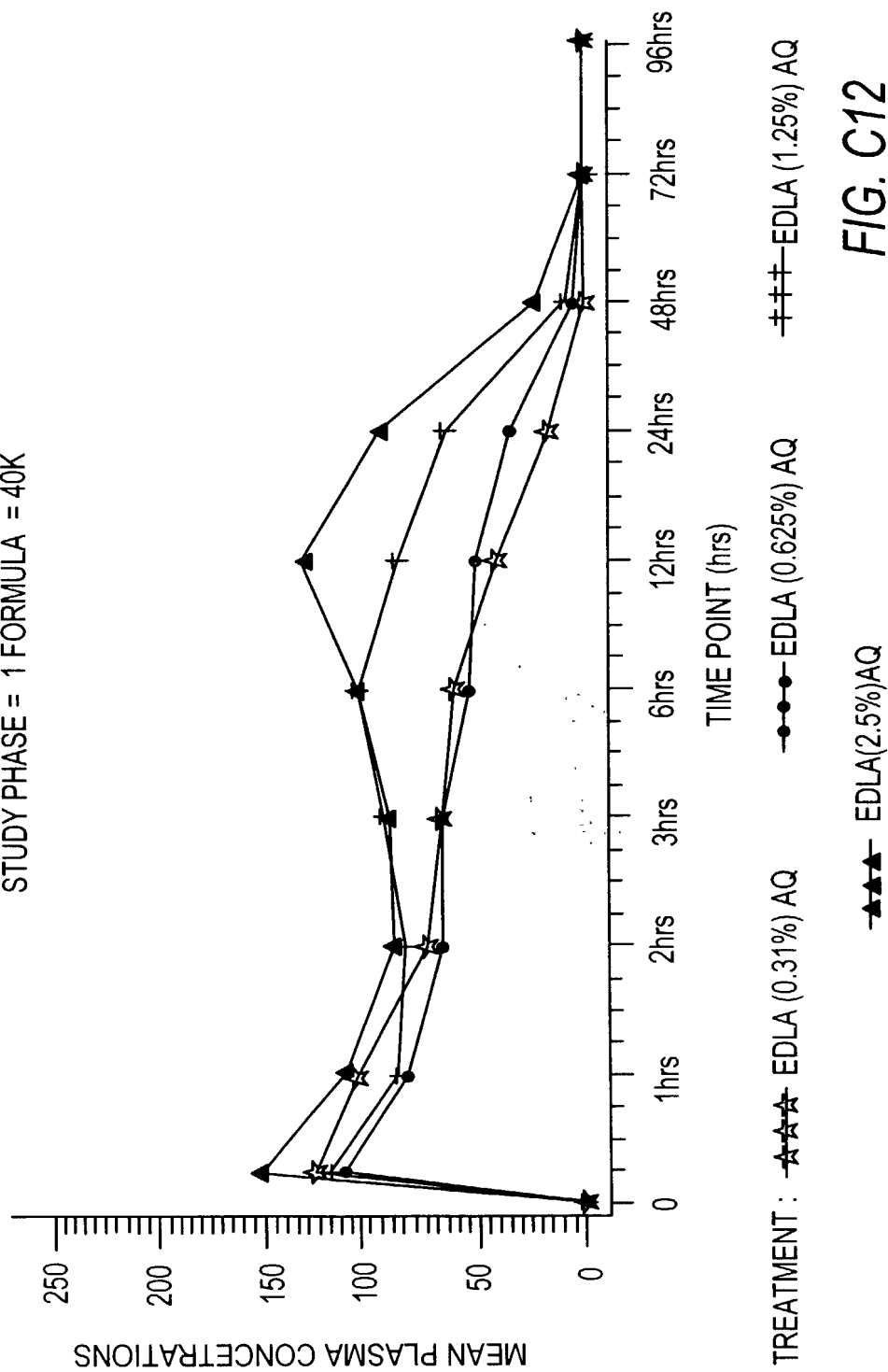


FIG. C12

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 2 FORMULA = 40K

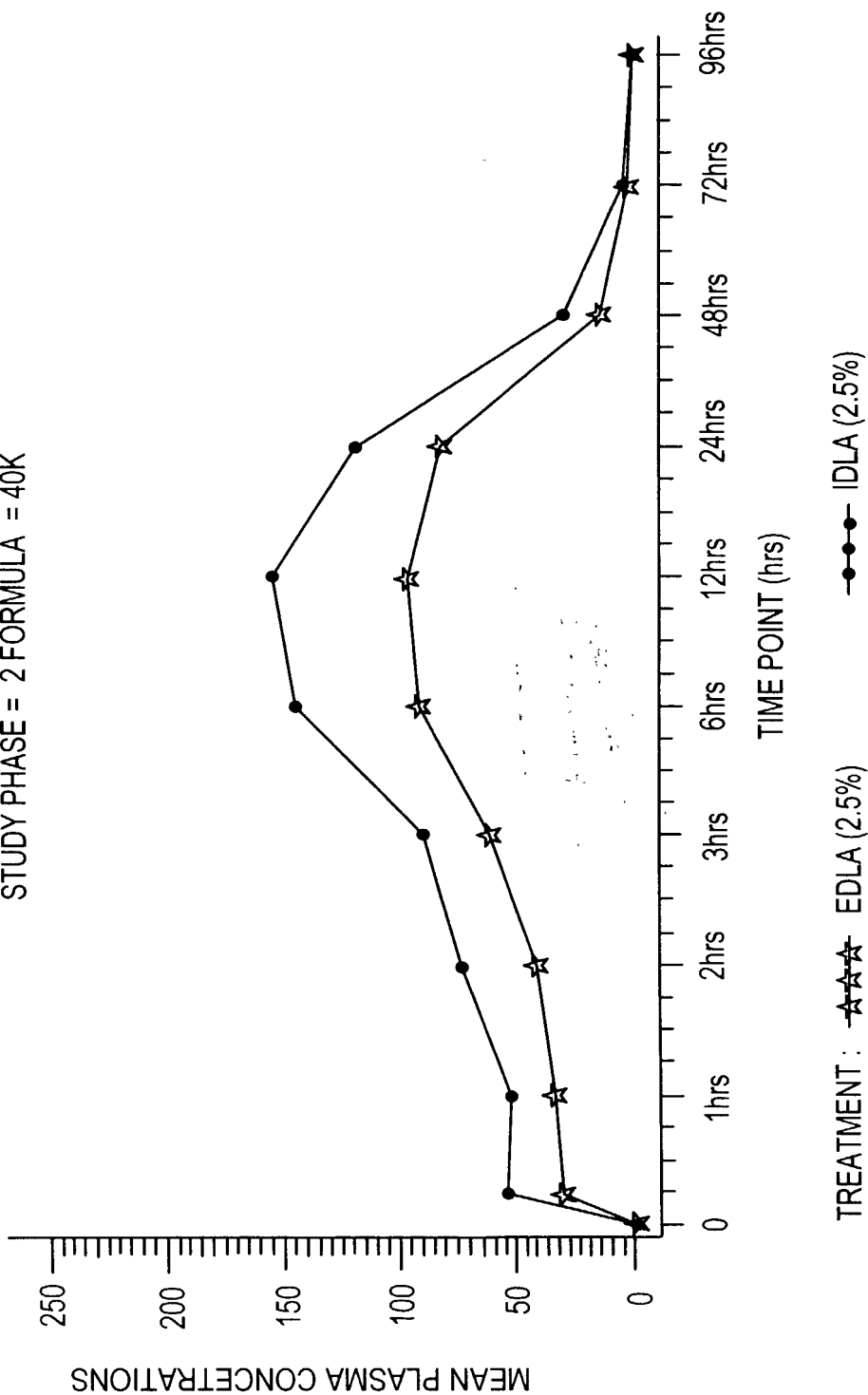
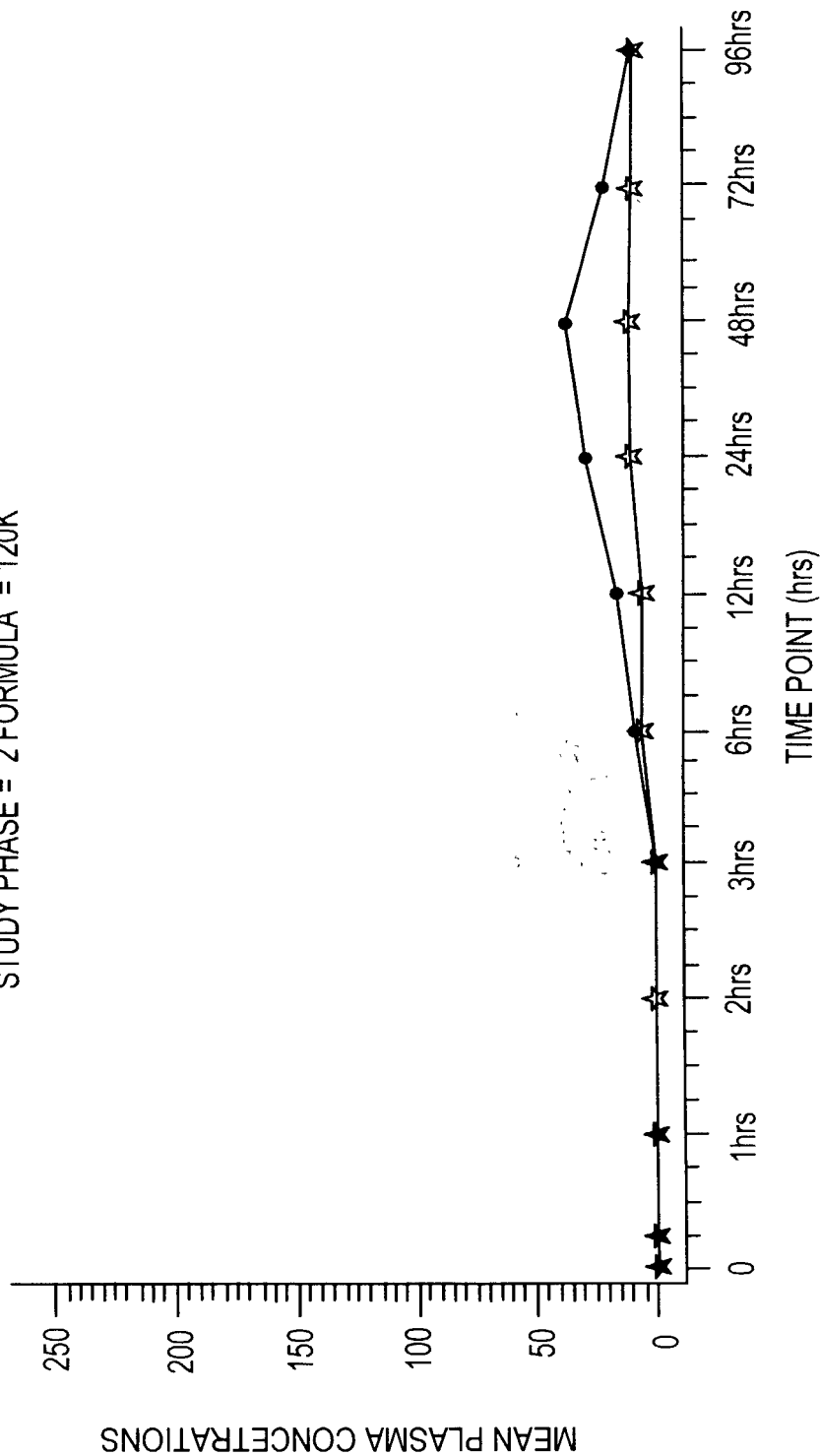


FIG. C13

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 2 FORMULA = 120K



TREATMENT : ★★ EDLA (1.25%) ●● IDLA (1.25%) **FIG. C14**

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT
 POPULATION: ALL SUBJECTS ENROLLED IN STUDY
 STUDY PHASE = 3 FORMULA = 40K

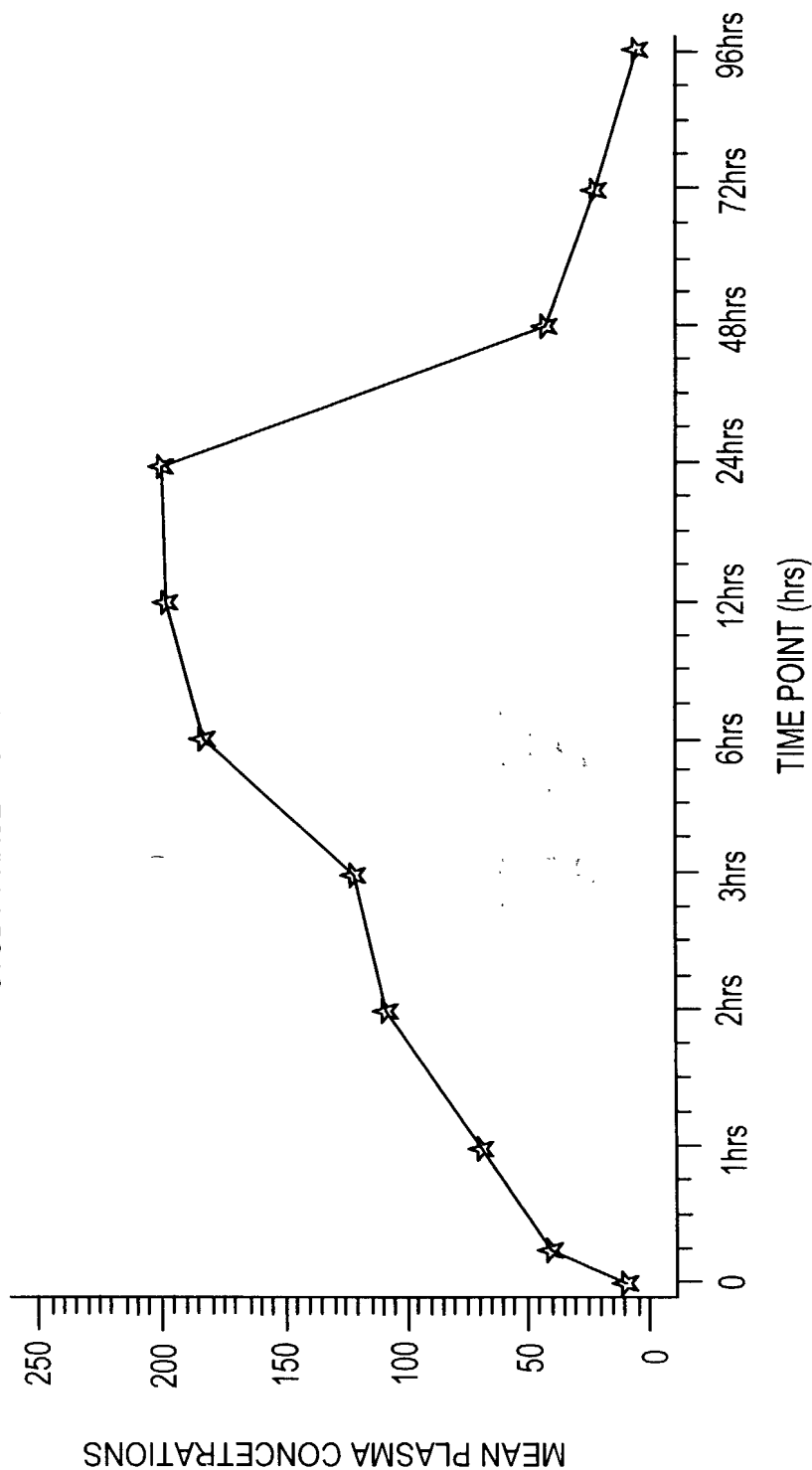


FIG. C15

TREATMENT : ★★ EDLA (5.0%)

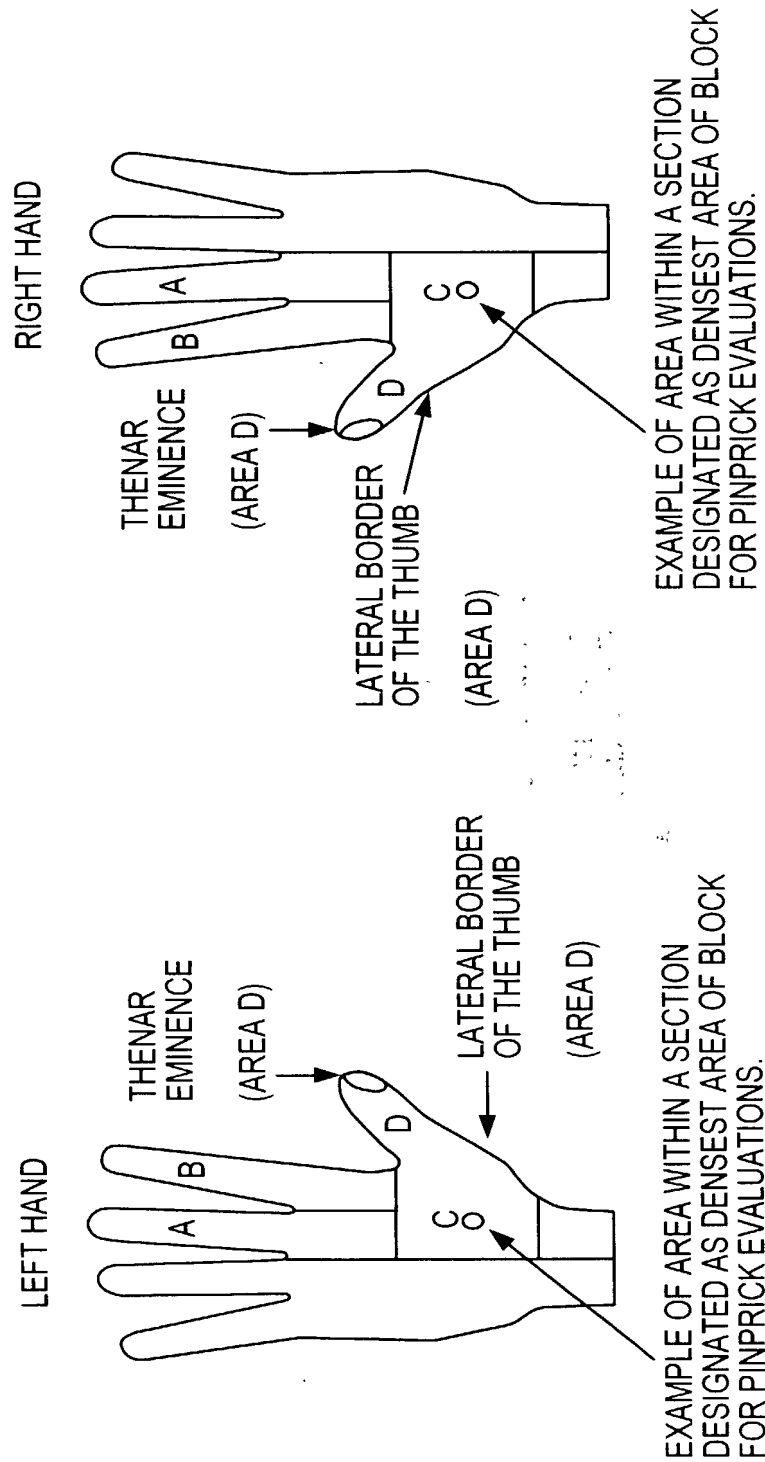
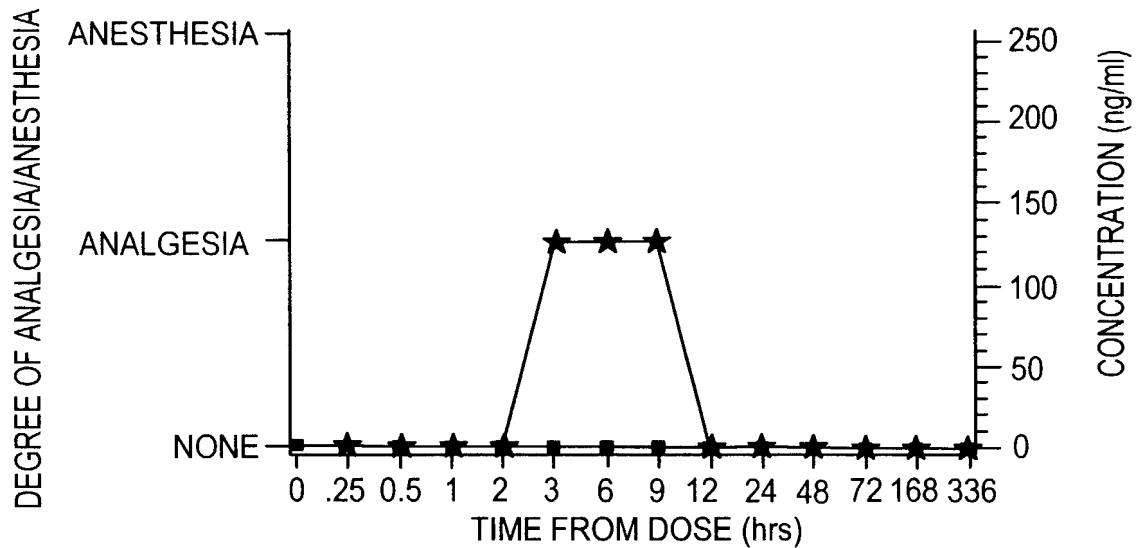


FIG. D1

33/ 57

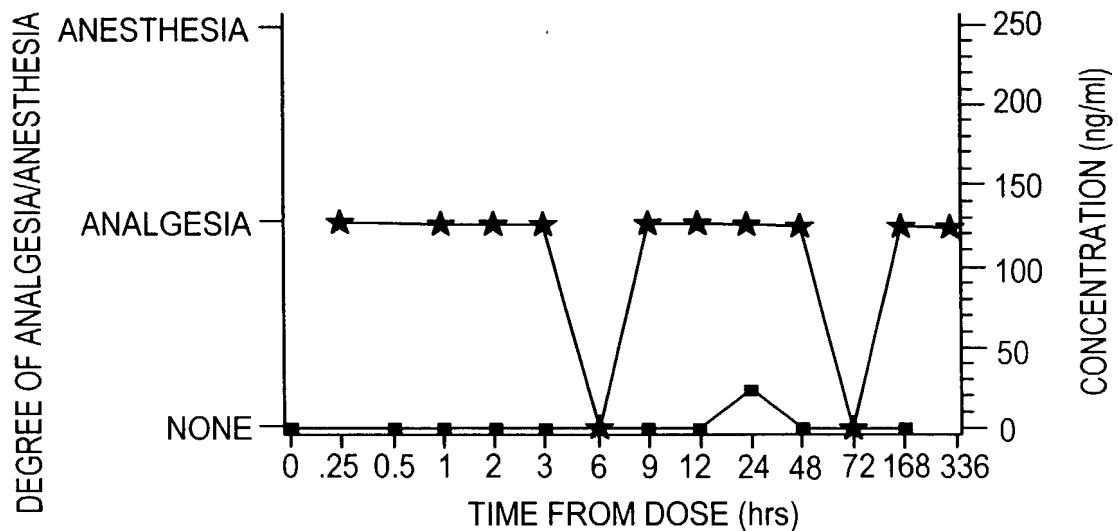
SUBJECT 1



13SEP99
CROSS REFERENCES;
APPENDIX 16.2.6.3

LEGEND: STAR -- ANALGESIA/ANESTHESIA
SQUARE -- CONCENTRATION

SUBJECT 3



13SEP99
CROSS REFERENCES;
APPENDIX 16.2.6.3

LEGEND: STAR -- ANALGESIA/ANESTHESIA
SQUARE -- CONCENTRATION

FIG. D2

DEGREE OF ANALGESIA/ANESTHESIA IN RELATION TO PLASMA BUPIVACAINE CONCENTRATIONS FOR EACH SUBJECT RECEIVING 2.5% 120K EDLA (N = 3)

34/ 57

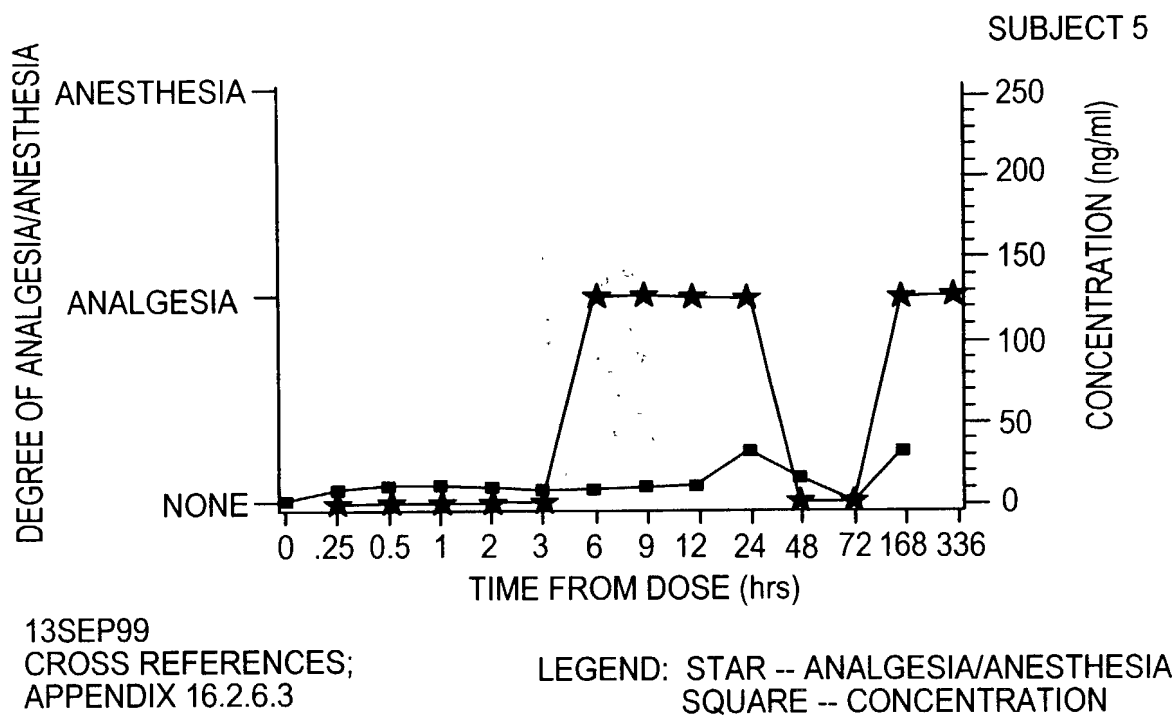
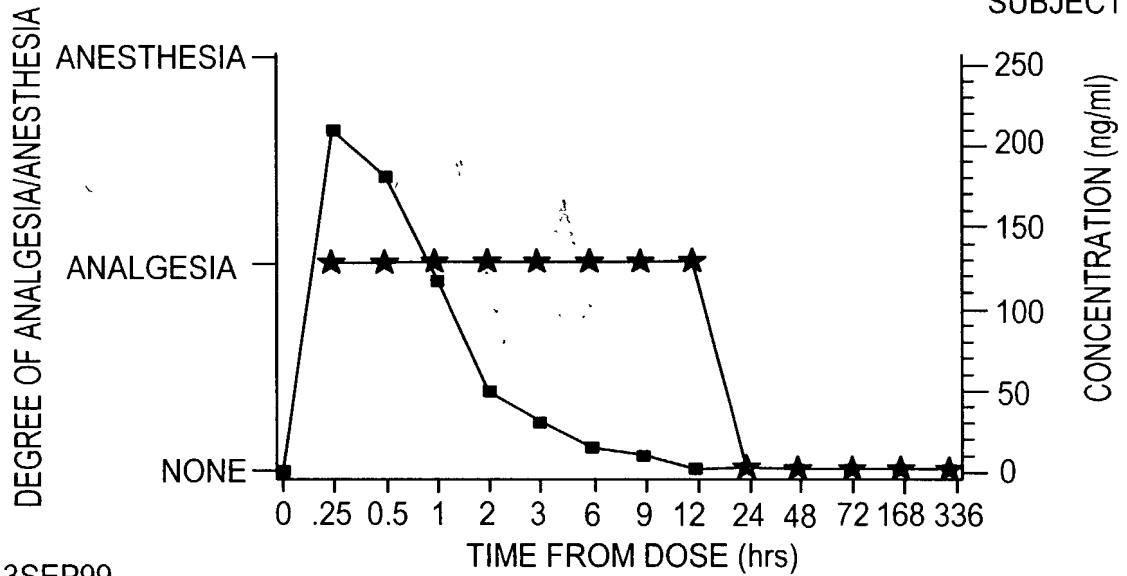


FIG. D2 (CONTINUED)

DEGREE OF ANALGESIA/ANESTHESIA IN RELATION TO PLASMA BUPIVACAINE CONCENTRATIONS FOR EACH SUBJECT RECEIVING 2.5% 120K EDLA (N = 3)

35/ 57

SUBJECT 2

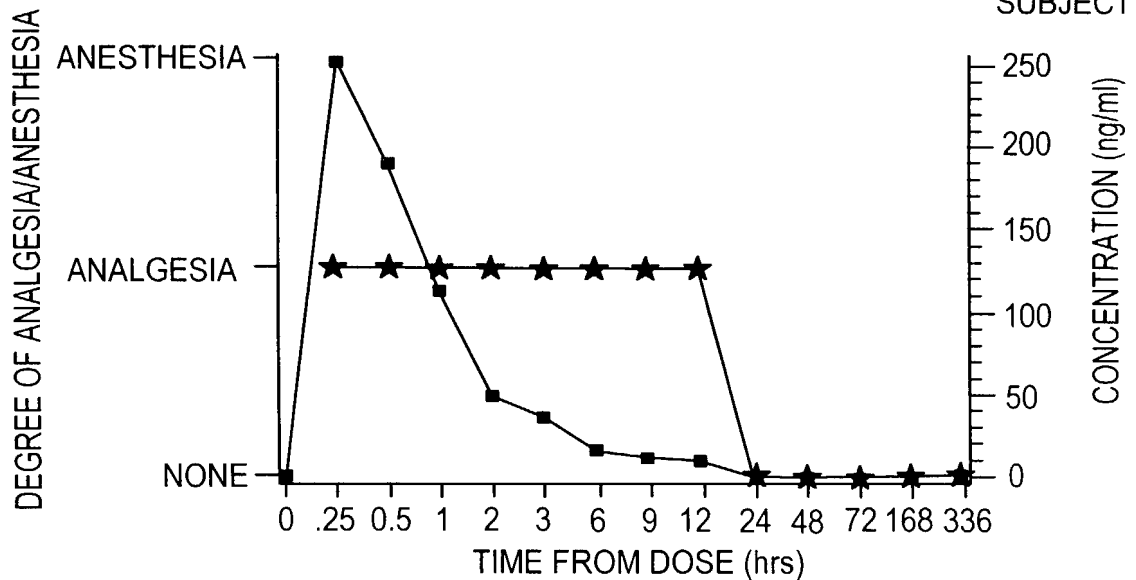


13SEP99

CROSS REFERENCES;
APPENDIX 16.2.6.3

LEGEND: STAR -- ANALGESIA/ANESTHESIA
SQUARE -- CONCENTRATION

SUBJECT 4



13SEP99

CROSS REFERENCES;
APPENDIX 16.2.6.3

LEGEND: STAR -- ANALGESIA/ANESTHESIA
SQUARE -- CONCENTRATION

FIG. D3

DEGREE OF ANALGESIA/ANESTHESIA IN RELATION TO PLASMA BUPIVACAINE
CONCENTRATIONS FOR EACH SUBJECT RECEIVING 0.5% AB-D (N = 3)

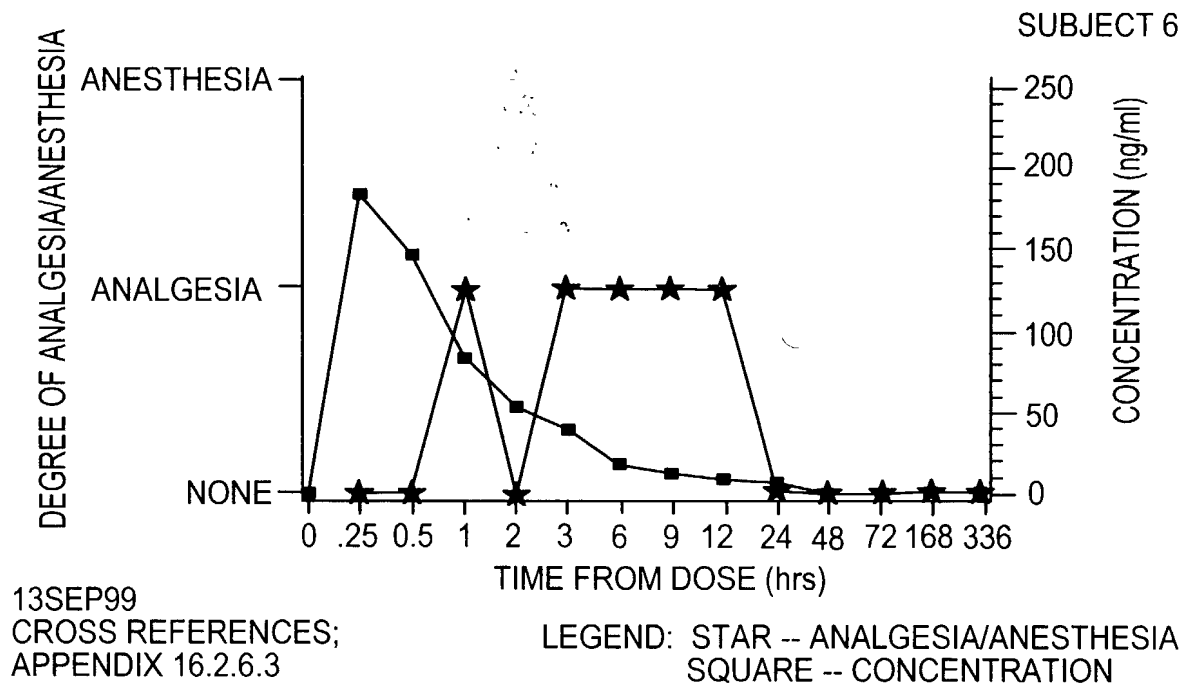


FIG. D3 (CONTINUED)

DEGREE OF ANALGESIA/ANESTHESIA IN RELATION TO PLASMA BUPIVACAINE CONCENTRATIONS FOR EACH SUBJECT RECEIVING 0.5% AB-D (N = 3)

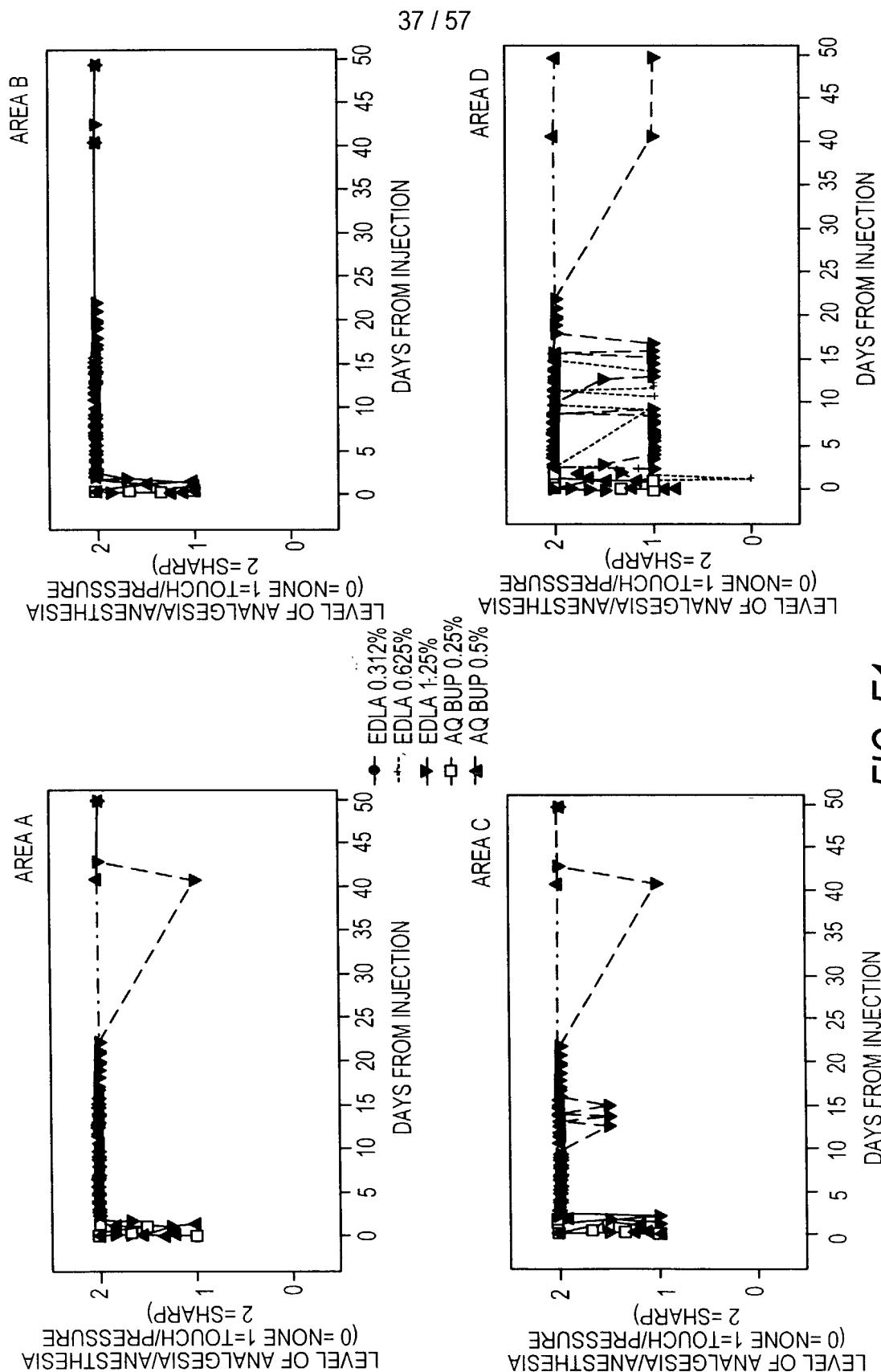
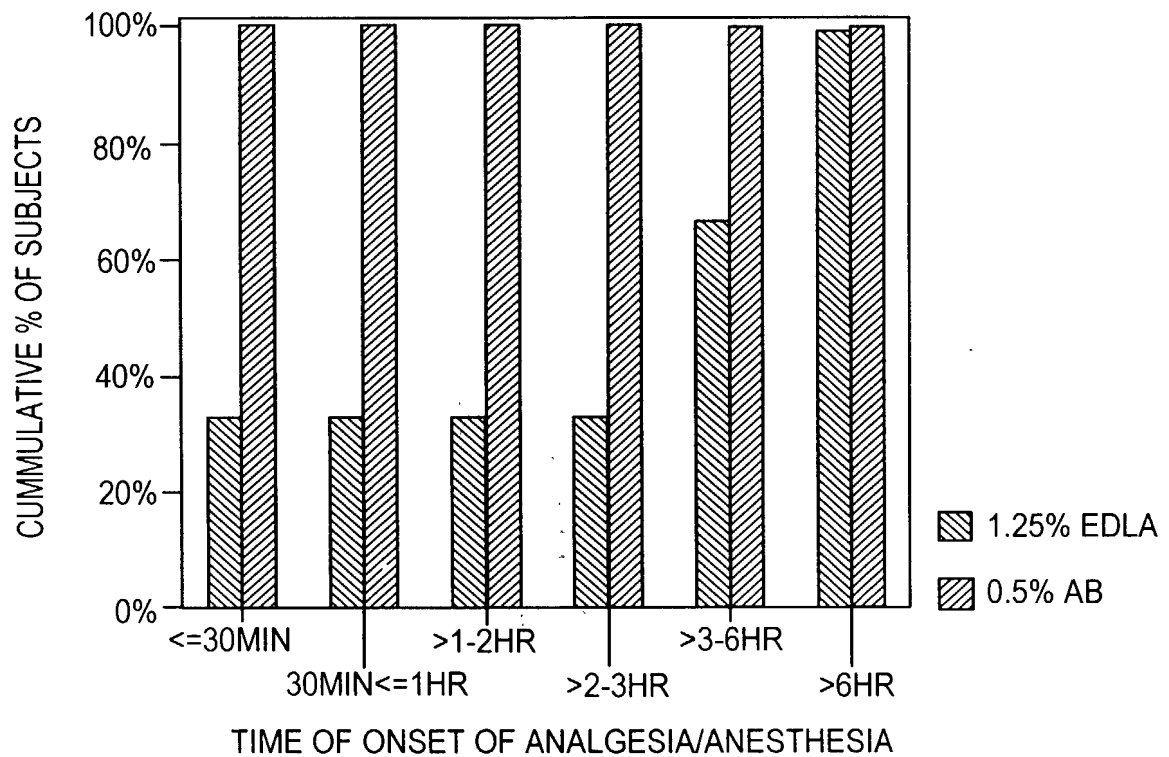


FIG. E1

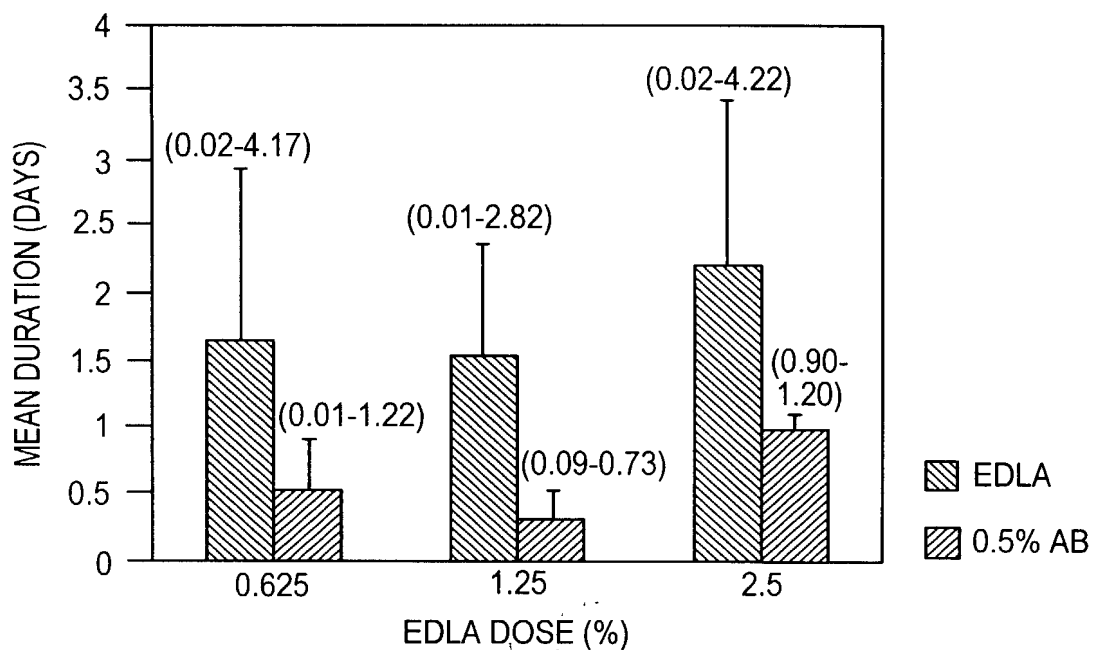
MEAN PINPRICK SCORE OVER TIME, BY EACH TREATMENT AND FOR EACH ASSESSMENT AREA

38 / 57

**FIG. F1**

CUMULATIVE PERCENT OF SUBJECTS DEMONSTRATING ONSET OF ANALGESIA/ ANESTHESIA WITHING 6 HOURS FOR 1.25% 40K EDLA VERSUS 0.5% AB

39 / 57



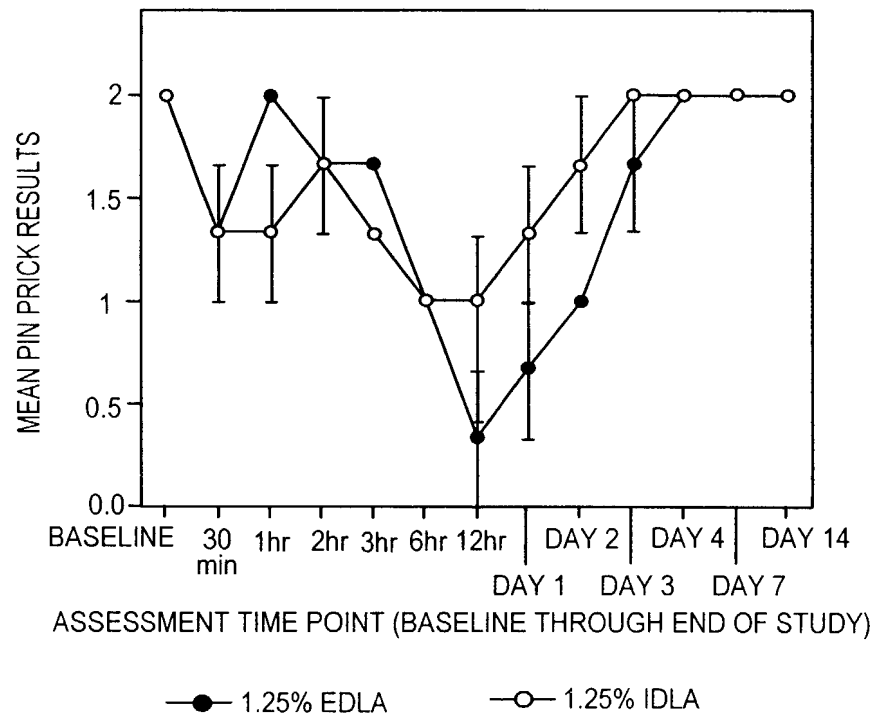
DURATION OF ANALGESIA/ANESTHESIA IN AREA C, BY DOSE
40K EDLA/AB
STUDY PART I

| | TREATMENT PAIR N=3 | | TREATMENT PAIR N=3 | | TREATMENT PAIR N=3 | |
|----------|-----------------------|------------|-----------------------|------------|-----------------------|------------|
| | 40K EDLA 0.625% | AB 0.5% | 40K EDLA 1.25% | AB 0.5% | 40K EDLA 2.5% | AB 0.5% |
| DURATION | | | | | | |
| MEAN | 1.65 | 0.53 | 1.53 | 0.33 | 2.23 | 1.00 |
| (SE) | (1.28) | (0.36) | (0.82) | (0.20) | (1.22) | (0.10) |
| RANGE | 0.02-4.17 | 0.01-1.22 | 0.01-2.82 | 0.09-0.73 | 0.02-4.22 | 0.90-1.20 |

MEAN (SE) AND RANGE OF DURATION OF ANALGESIA/ANESTHESIA BY
DOSE FOR 40K EDLA VERSUS 0.5% AB

FIG. F2

40 / 57



| | BASE -LINE | 30 min | Hr 1 | Hr 2 | Hr 3 | Hr 6 | Hr 12 | DAY 1 ^b | DAY 2 ^b | DAY 3 ^b | DAY 4 ^b | DAY 7 ^b | DAY 14 ^b |
|--|---------------|-----------|---------|---------|---------|---------|----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|------------------------|
| PINPRICK TEST RESULTS ^a 1.25% 40K EDLA N=3 | | | | | | | | | | | | | |
| MEAN | 2 | 1.33 | 2 | 1.67 | 1.67 | 1 | 0.33 | 0.67 | 1 | 1.67 | 2 | 2 | 2 |
| (SE) | (0) | (0.33) | (0) | (0.33) | (0.33) | (0) | (0.33) | (0.33) | (0) | (0.33) | (0) | (0) | (0) |
| RANGE | 2-2 | 1-2 | 2-2 | 1-2 | 1-2 | 1-1 | 0-1 | 0-1 | 1-1 | 1-2 | 2-2 | 2-2 | 2-2 |
| PINPRICK TEST RESULTS ^a 1.25% 40K IDLA N=3 | | | | | | | | | | | | | |
| MEAN | 2 | 1.33 | 1.33 | 1.67 | 1.33 | 1 | 1 | 1.33 | 1.67 | 2 | 2 | 2 | 2 |
| (SE) | (0) | (0.33) | (0.33) | (0.33) | (0.33) | (0) | (0.58) | (0.33) | (0.33) | (0) | (0) | (0) | (0) |
| RANGE | 2-2 | 1-2 | 1-2 | 1-2 | 1-2 | 1-1 | 0-2 | 1-2 | 1-2 | 2-2 | 2-2 | 2-2 | 2-2 |

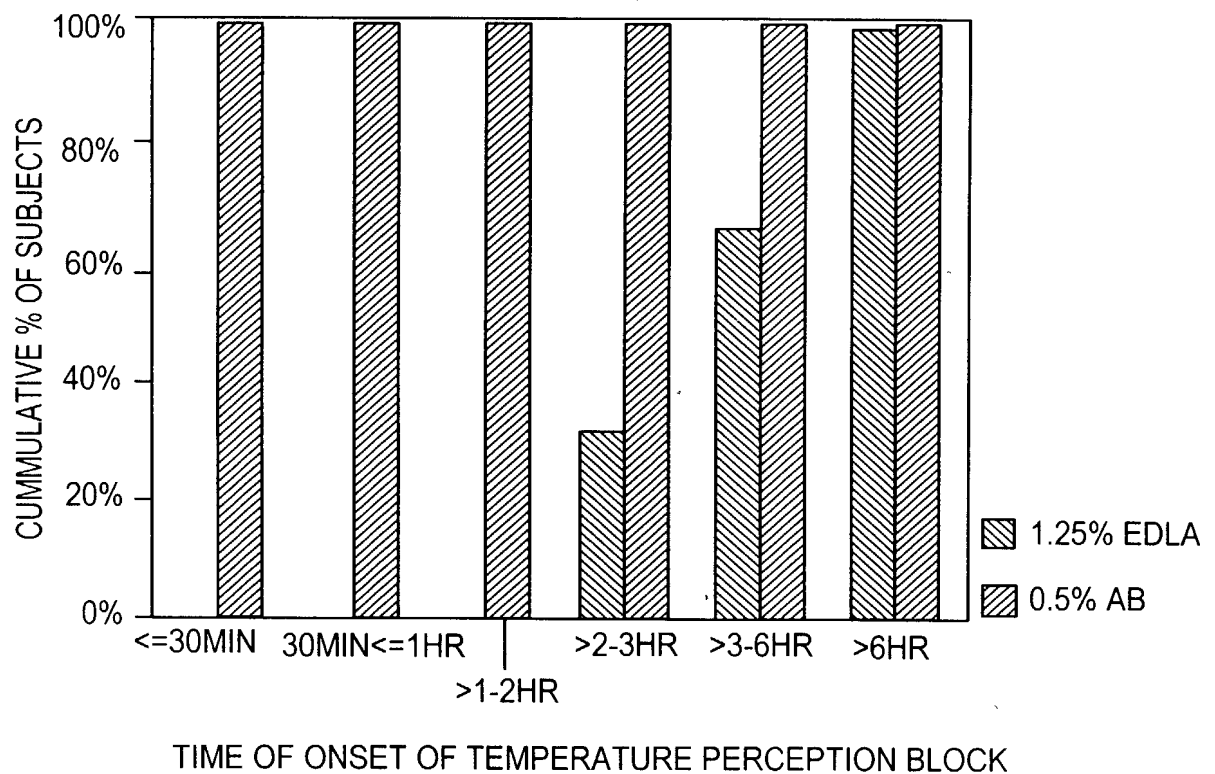
^aEVALUATED ON A SCALE OF 0-2, WITH 0 = NO FEELING;
1 = FEELS TOUCH/PRESSURE; 2 = FEELS SHARP.

^bAFTERNOON INVESTIGATOR RESULTS

TIME COURSE OF ANALGESIA/ANESTHESIA IN AREA C FOR 1.25% 40K EDLA
VERSUS 1.25% 40K IDLA

FIG. F3

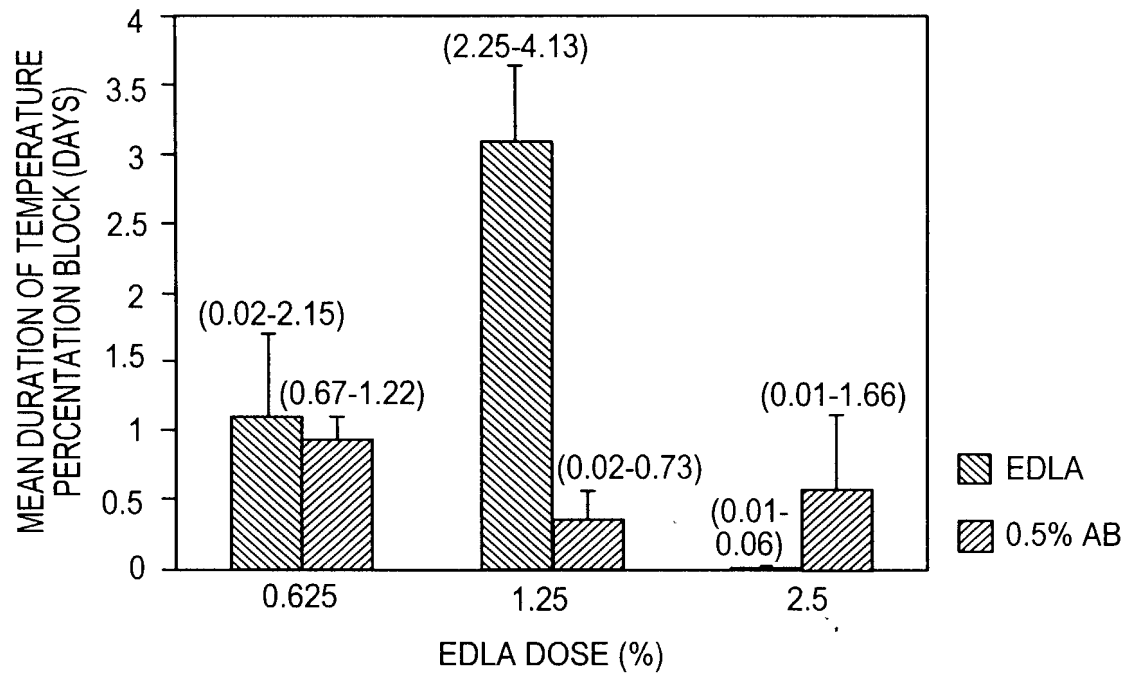
41 / 57



CUMMALATIVE PERCENT OF SUBJECTS DEMOSTRATING TEMPERATURE PERCEPTION BLOCK WITHIN 6 HOURS FOR 1.25% 40K EDLA VERSUS 0.5% AB

FIG. F4

42 / 57

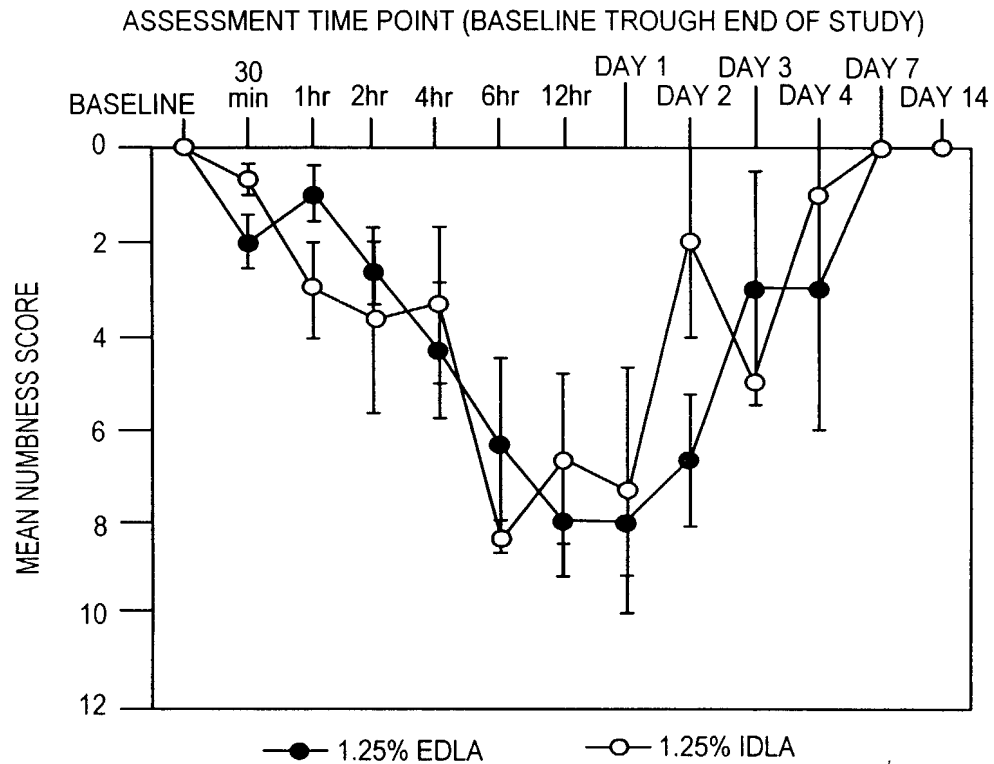


| DURATION OF TEMPERATURE PERCEPTION BLOCK 40K EDLA/AB | | | | | | |
|---|--------------------|------------|-------------------|------------|------------------|------------|
| DURATION (DAYS) | TREATMENT PAIR | | TREATMENT PAIR | | TREATMENT PAIR | |
| | 40K EDLA 0.625% | AB 0.5% | 40K EDLA 1.25% | AB 0.5% | 40K EDLA 2.5% | AB 0.5% |
| MEAN | 1.11 | 0.95 | 3.10 | 0.37 | 0.03 | 0.61 |
| (SE) | (0.61) | (0.16) | (0.55) | (0.21) | (0.01) | (0.52) |
| RANGE | 0.02-2.15 | 0.67-1.22 | 2.25-4.13 | 0.02-0.73 | 0.01-0.06 | 0.01-1.66 |

MEAN (SE) AND OF DURATION (DAYS) OF TEMPERATURE
PERCEPTION BLOCK IN AREA C FOR 40K EDLA BY DOSE

FIG. F5

43 / 57



| | BASE -LINE | 30 min | Hr 1 | Hr 2 | Hr 3 | Hr 6 | Hr 12 | DAY 1 ^b | DAY 2 ^b | DAY 3 ^b | DAY 4 ^b | DAY 7 ^b | DAY 14 ^b |
|---|---------------|-----------|---------|---------|---------|---------|----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|------------------------|
| 1.25% 40K EDLA N=3 | | | | | | | | | | | | | |
| LEVEL OF NUMBNESS TEST RESULTS ^a | | | | | | | | | | | | | |
| MEAN | 0 | 2 | 1 | 2.67 | 4.33 | 6.33 | 8 | 8 | 6.67 | 3 | 3 | 0 | 0 |
| (SE) | (0) | (0.58) | (0.58) | (0.67) | (1.45) | (1.86) | (1.15) | (1.15) | (1.45) | (2.52) | (3) | (0) | (0) |
| RANGE | 0-0 | 1-3 | 0-2 | 2-4 | 2-7 | 4-10 | 6-10 | 6-10 | 4-9 | 0-8 | 0-6 | 0-0 | 0-0 |
| 1.25% 40K IDLA N=3 | | | | | | | | | | | | | |
| LEVEL OF NUMBNESS TEST RESULTS ^a | | | | | | | | | | | | | |
| MEAN | 0 | 0.67 | 3 | 3.67 | 3.33 | 8.33 | 6.67 | 7.33 | 2 | 5 | 1 | 0 | 0 |
| (SE) | (0) | (0.33) | (1) | (2.03) | (1.67) | (0.33) | (1.86) | (2.67) | (2) | (0) | (0) | (0) | (0) |
| RANGE | 0-0 | 0-1 | 1-4 | 0-7 | 0-5 | 8-9 | 3-9 | 2-10 | 0-6 | 5-5 | 1-1 | 0-0 | 0-0 |

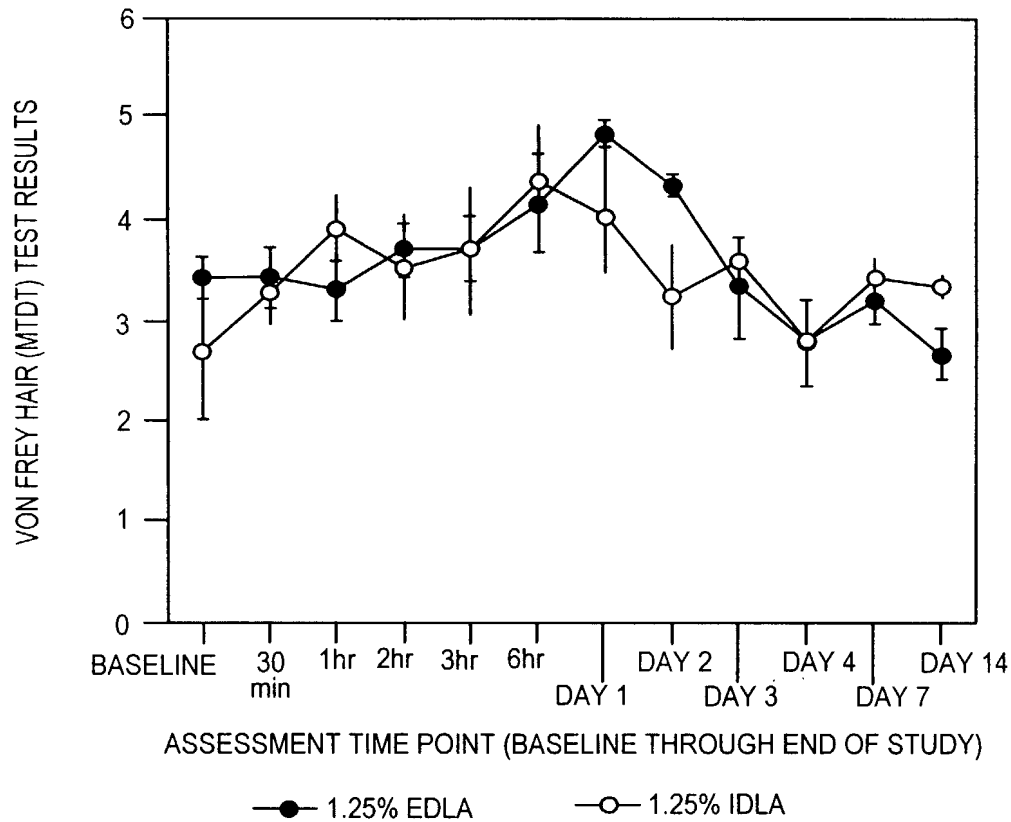
^aEVALUATED ON A SCALE OF 0-10, WITH 0 = NOT NUMB AT ALL, AND 10 = TOTALLY NUMB.

^bAFTERNOON INVESTIGATOR RESULTS

TIME COURSE OF NUMBNESS FOR 1.25% 40K EDLA
VERSUS 1.25% 40K IDLA IN AREA C

FIG. F6

44 / 57



| | BASE | 30 | Hr | Hr | Hr | Hr | DAY | DAY | DAY | DAY | DAY | DAY |
|-----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|----------------|----------------|----------------|----------------|----------------|-----------------|
| | -LINE | min | 1 | 2 | 3 | 6 | 1 ^b | 2 ^b | 3 ^b | 4 ^b | 7 ^b | 14 ^b |
| 1.25% 40K EDLA N=3 | | | | | | | | | | | | |
| VON FREY HAIR (MTDT) TEST RESULTS | | | | | | | | | | | | |
| MEAN | 3.43 | 3.43 | 3.3 | 3.71 | 3.71 | 4.17 | 4.85 | 4.35 | 3.35 | 2.79 | 3.22 | 2.67 |
| (SE) | (0.21) | (0.31) | (0.29) | (0.26) | (0.32) | (0.48) | (0.11) | (0.11) | (0.51) | (0.43) | (0.23) | (0.27) |
| RANGE | 3.22-3.84 | 2.83-3.84 | 2.83-3.84 | 3.22-4.08 | 3.22-4.31 | 3.22-4.74 | 4.74-5.07 | 4.17-4.56 | 2.36-4.08 | 2.36-3.22 | 2.83-3.61 | 2.36-3.22 |
| 1.25% 40K IDLA N=3 | | | | | | | | | | | | |
| VON FREY HAIR (MTDT) TEST RESULTS | | | | | | | | | | | | |
| MEAN | 2.7 | 3.3 | 3.9 | 3.54 | 3.72 | 4.36 | 4.04 | 3.25 | 3.61 | 2.83 | 3.43 | 3.35 |
| (SE) | (0.52) | (0.29) | (0.34) | (0.52) | (0.65) | (0.57) | (0.8) | (0.52) | (0) | (0) | (0.21) | (0.13) |
| RANGE | 1.65-3.22 | 2.83-3.84 | 3.22-4.31 | 2.83-4.56 | 2.44-4.56 | 3.22-4.93 | 2.44-4.93 | 2.36-4.17 | 3.61-3.61 | 2.83-2.83 | 3.22-3.84 | 3.22-3.61 |

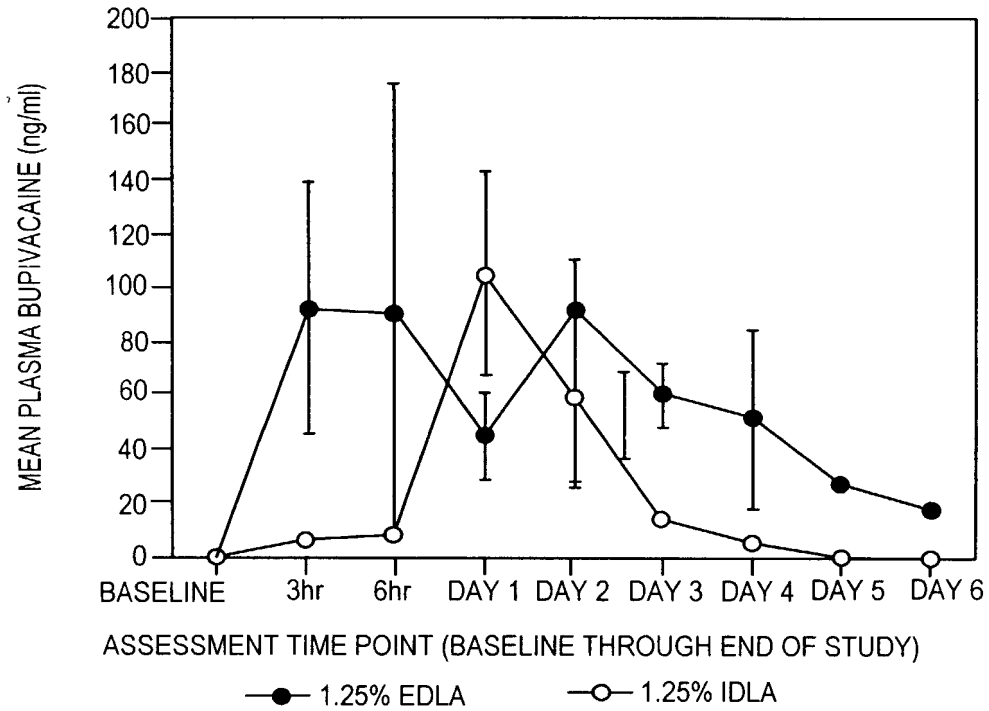
^aEVALUATED ON A SCALE OF 1.65 TO 7 WITH 1.65 BEING THE LOWEST VON FREY HAIR NUMERICAL DESIGNATION AND A SCORE OF 7 GIVEN IF THE HIGHEST VON FREY HAIR NUMERICAL DESIGNATION OF 6.65 DOES NOT PRODUCE ANY SENSATION OF TOUCH.

^bAFTERNOON INVESTIGATOR RESULTS

TIME COURSE OF VON FREY HAIR TEST RESULTS (MTDT) FOR 1.25% 40K EDLA VERSUS 1.25% 40K IDLA IN AREA C

FIG. F7

45 / 57



| | BASE -LINE | Hr 3 | Hr 6 | DAY 1 | DAY 2 | DAY 3 | DAY 4 | DAY 5 | DAY 6 |
|-----------------------------------|---------------|---------|-----------|----------|----------|-----------|-----------|-----------|-------|
| 1.25% 40K EDLA N=3 | | | | | | | | | |
| PLASMA BUPIVACAINE RESULTS | | | | | | | | | |
| MEAN (ng/ml) | 0 | 92.67 | 91.55 | 45.73 | 93.8 | 61.27 | 52.85 | 28.2 | 19 |
| (SE) | (0) | (46.77) | (85.23) | (16.51) | (66.43) | (12.33) | (33.45) | (0) | (0) |
| RANGE | 0.0 | 0-150 | 5.48-262 | 13-65.9 | 10.1-225 | 37.1-77.6 | 19.4-86.3 | 28.2-28.2 | 19-19 |
| 1.25% 40K IDLA N=3 | | | | | | | | | |
| VON FREY HAIR (MTDT) TEST RESULTS | | | | | | | | | |
| MEAN (ng/ml) | 0 | 5.95 | 8.9 | 106.03 | 60.23 | 14.8 | 6.28 | N.D. | N.D. |
| (SE) | (0) | (3.56) | (1.95) | (38.18) | (34.06) | (0) | (0) | N.D. | N.D. |
| RANGE | 0.0 | 0-12.3 | 6.01-12.6 | 30.1-151 | 20.3-128 | 14.8-14.8 | 6.28-6.28 | N.D. | N.D. |

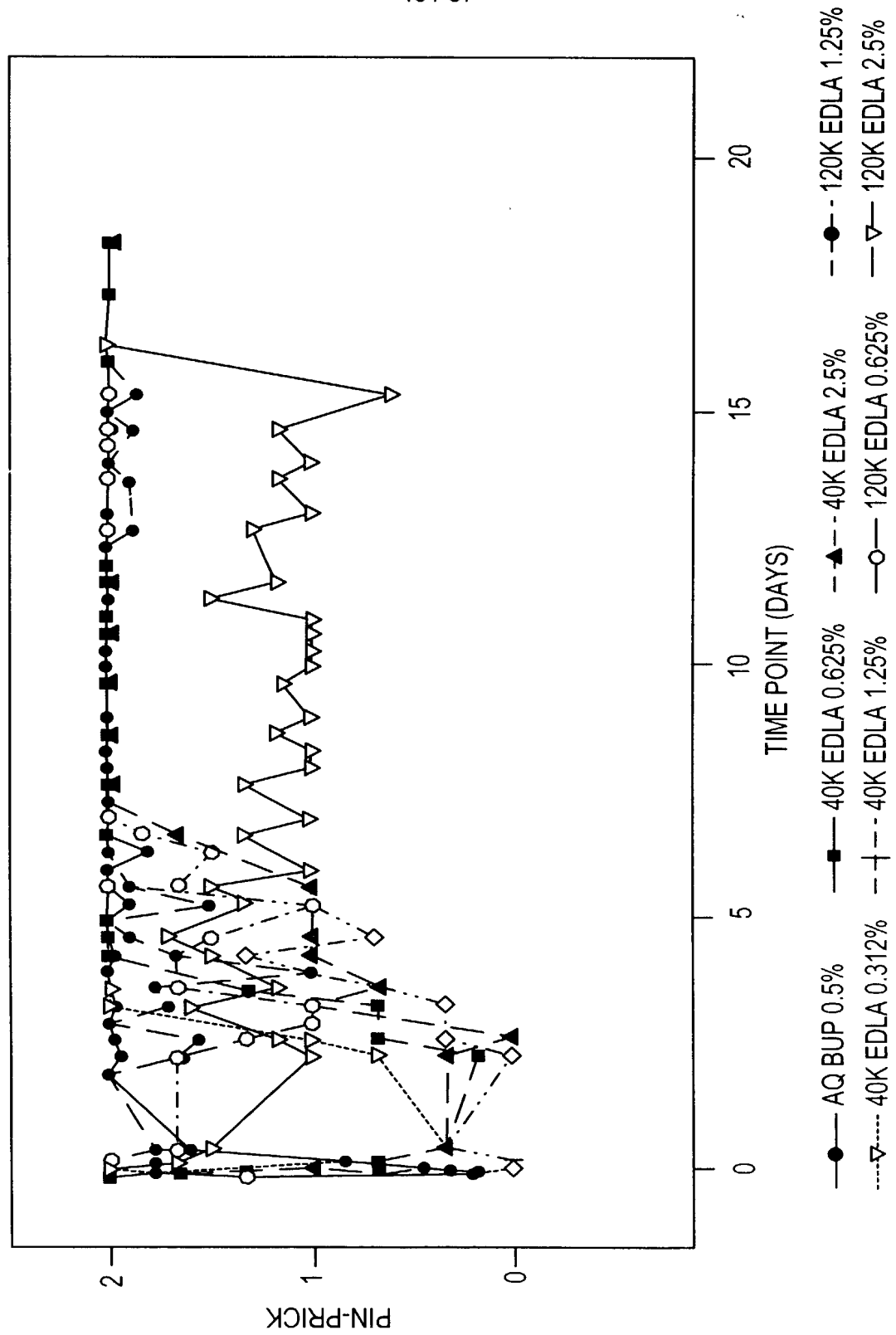
N.D.-NOT DETECTABLE

MEAN PLASMA BUPIVACAINE CONCENTRATION OVER TIME (1.25% 40K EDLA AND 1.25% 40K IDLA, VOLUME=3 mL)

FIG. F8

FIG. G1

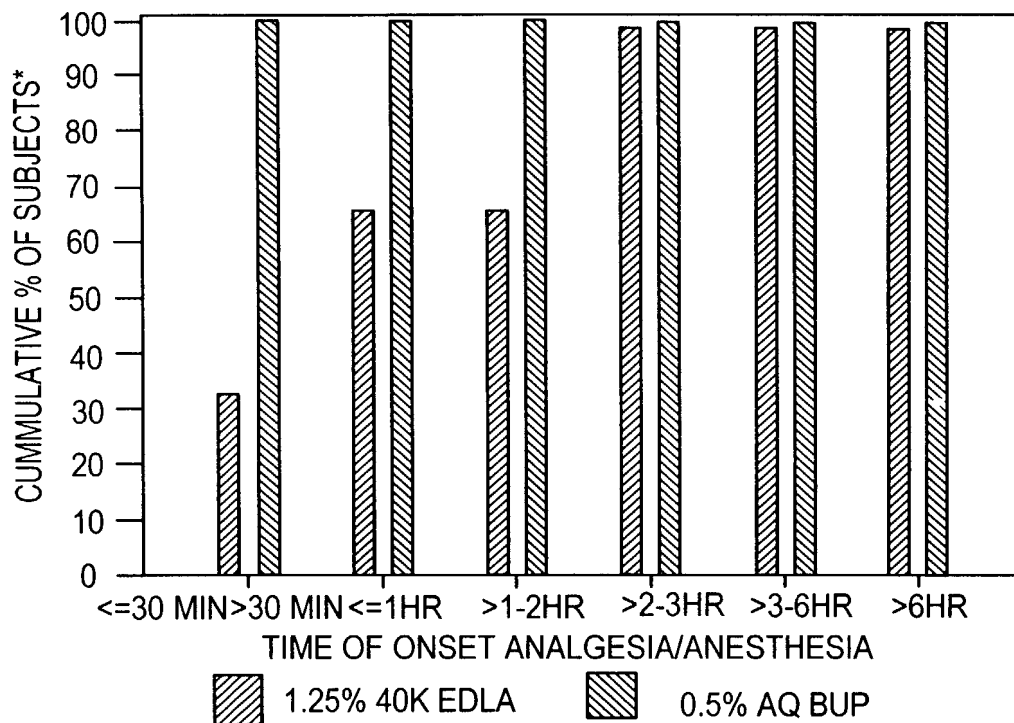
MEAN LEVEL OF ANALGESIA/ANESTHESIA OVER TIME PART I



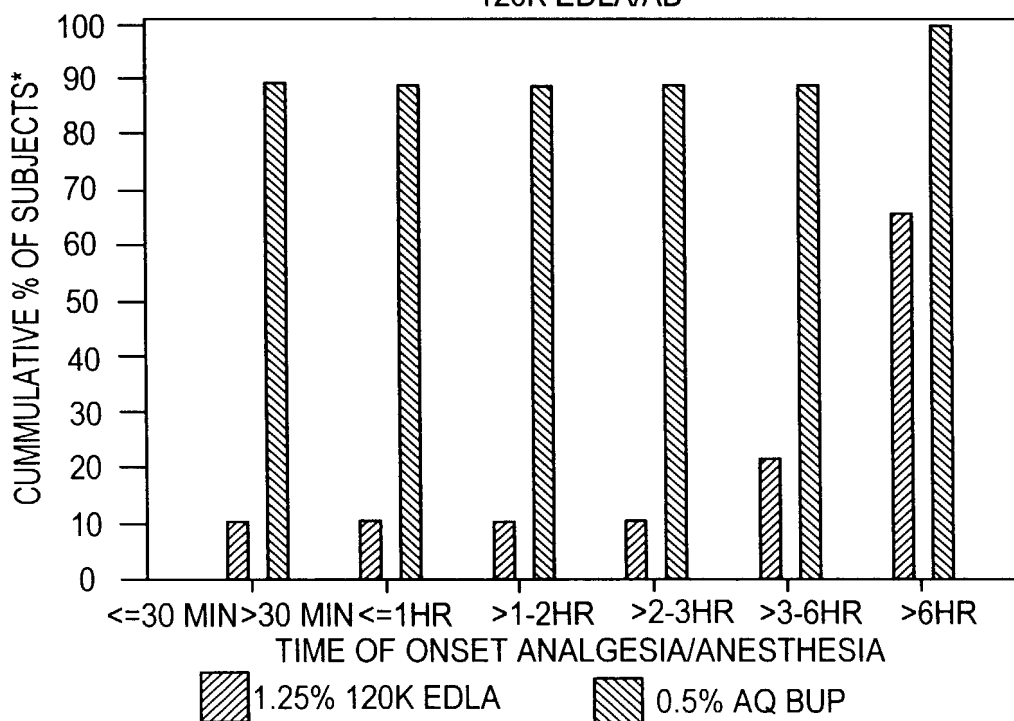
47 / 57

40K EDLA/AB

FIG. G2



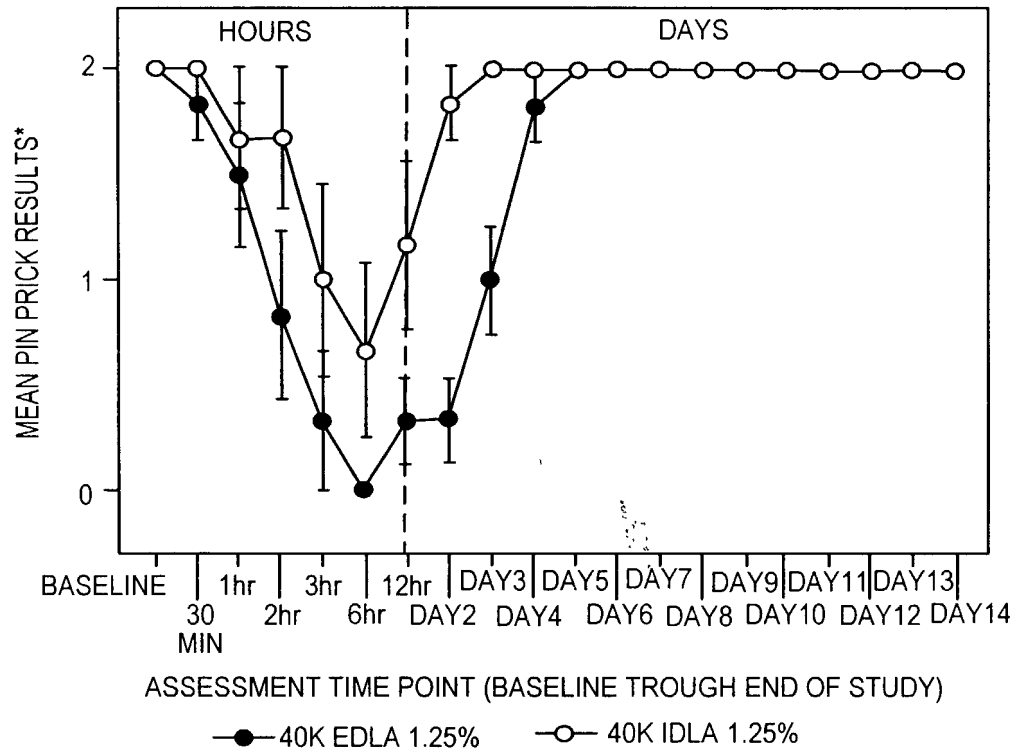
120K EDLA/AB



CUMMULATIVE PERCENT OF SUBJECTS DEMONSTRATING ONSET OF ANALGESIA/ANESTHESIA WITHIN 6 HOURS FOR 1.25% 40K AND 120K EDLA vs AB

*EACH TIME POINT REPRESENTS AN ACCUMULATION UNTIL THE HIGHEST GROUP VALUE ACHIEVED

48 / 57



| | BASE -LINE | 30 min | h1 | h2 | h3 | h6 | h12 | DAY 2 | DAY 3 | DAY 4 | DAY 5 | DAY 6 | DAY 7 |
|------------------------------|------------------|-----------|-------|-------|-------|-------|-------|----------|----------|----------|----------|----------|----------|
| PINPRICK SCORES ^b | | | | | | | | | | | | | |
| | 40K EDLA 1.25% | | | | | | | | | | | | |
| | N=6 ^a | | | | | | | | | | | | |
| MEAN | 2 | 1.8 | 1.5 | 0.8 | 0.4 | 0 | 0.3 | 0 | 1.0 | 1.8 | 2.0 | 2.0 | 2.0 |
| (SE) | (0) | (0.2) | (0.3) | (0.4) | (0.3) | (0) | (0.2) | (0) | (0.3) | (0.2) | (0) | (0) | (0) |
| RANGE | 2,2 | 1,2 | 0,2 | 0,2 | 0,2 | 0,0 | 0,1 | 0,1 | 0,2 | 1,2 | 2,2 | 2,2 | 2,2 |
| PINPRICK SCORES ^b | | | | | | | | | | | | | |
| | 40K IDLA 1.25% | | | | | | | | | | | | |
| | N=6 | | | | | | | | | | | | |
| MEAN | 2 | 2 | 1.7 | 1.7 | 1.0 | 0.7 | 1.2 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| (SE) | (0) | (0) | (0.3) | (0.3) | (0.5) | (0.4) | (0.4) | (0) | (0) | (0) | (0) | (0) | (0) |
| RANGE | 2,2 | 2,2 | 0,2 | 0,2 | 0,2 | 0,2 | 0,2 | 1,2 | 2,2 | 2,2 | 2,2 | 2,2 | 2,2 |

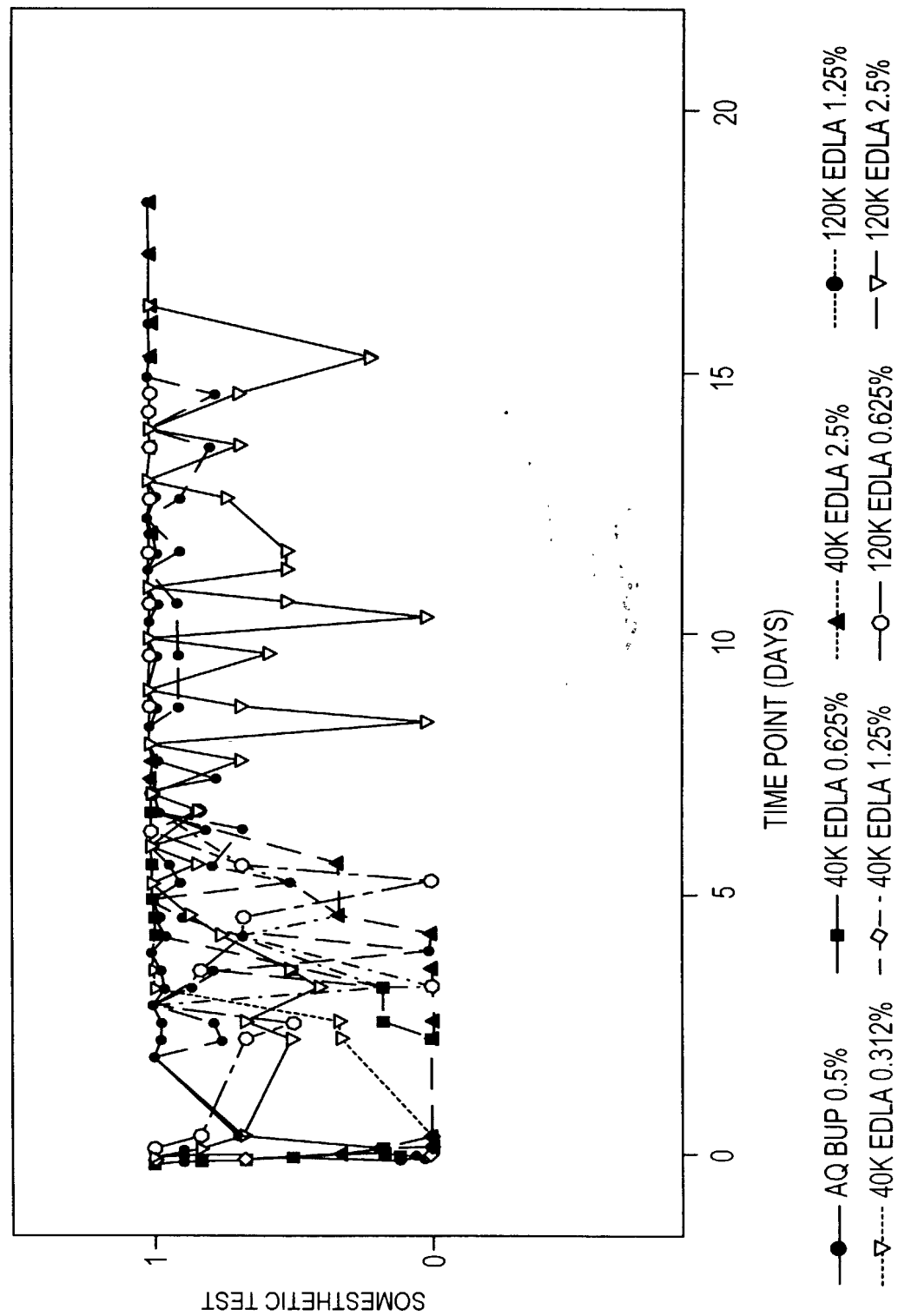
^a EDLA AND IDLA BLOCKS WERE ADMINISTERED BILATERALLY TO 6 SUBJECTS WHO RECEIVED ONE TREATMENT IN ONE FOOT AND THE OTHER TREATMENT IN THE OPPOSITE FOOT

^b EVALUATED ON A SCALE OF 0-2, WITH 0=NO FEELING;
1=FEELS TOUCH/PRESSURE; 2=FEELS SHARP

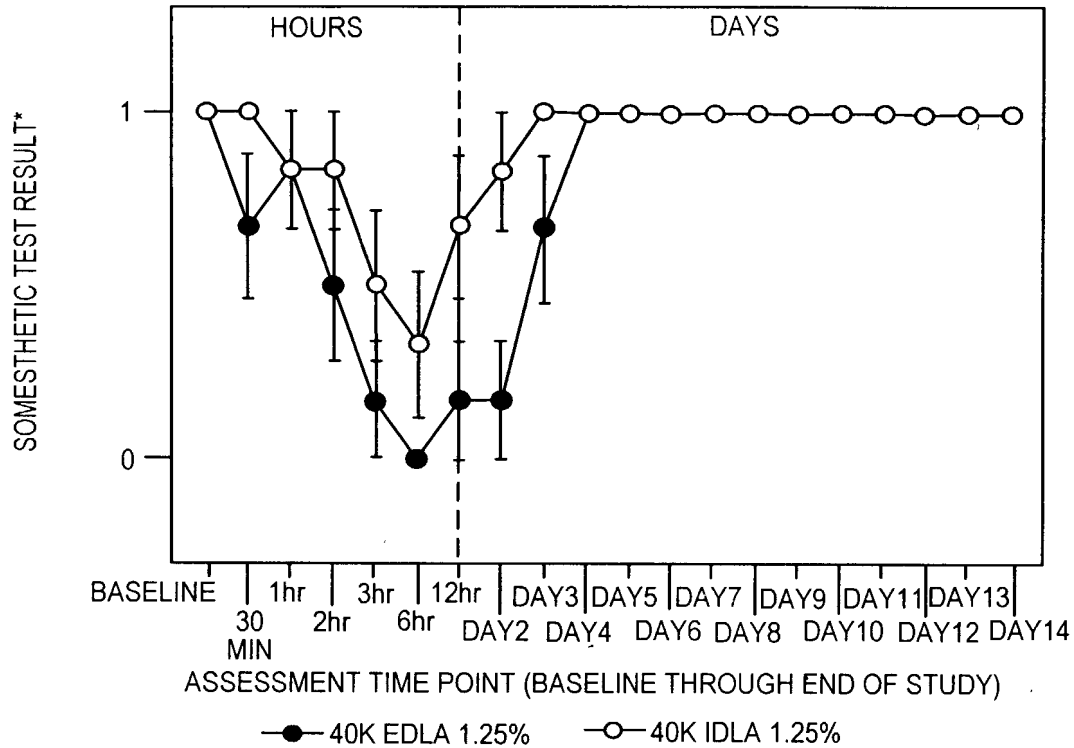
MEAN (SE) AND RANGE OF PINPRICK SCORES OVER TIME FOR 1.25% 40K EDLA vs
1.25% 40K IDLA

FIG. G3

MEAN LEVEL OF TEMPERATURE PERCEPTION BLOCKADE OVER TIME FOR TREATMENTS
 COMBINED - TOP OF FOOT PART I **FIG. G4**



50 / 57



| | BASE -LINE | 30 min | h1 | h2 | h3 | h6 | h12 | DAY 2 ^b | DAY 3 ^b | DAY 4 ^b | DAY 5 ^b | DAY 6 ^b | DAY 7 ^b |
|---|---------------|-----------|-------|-------|-------|-------|-------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| TEMPERATURE PERCEPTION SCORE ^a 40K EDLA 1.25% N=6 | | | | | | | | | | | | | |
| MEAN | 1 | 0.7 | 0.8 | 0.5 | 0.2 | 0 | 0.2 | 0.2 | 0.7 | 1.0 | 1.0 | 1.0 | 1.0 |
| (SE) | (0) | (0.2) | (0.2) | (0.2) | (0.2) | (0) | (0.2) | (0.2) | (0.2) | (0) | (0) | (0) | (0) |
| RANGE | 1,1 | 1,1 | 0,1 | 0,1 | 0,1 | 0,0 | 0,1 | 0,1 | 0,1 | 1,1 | 1,1 | 1,1 | 1,1 |
| TEMPERATURE PERCEPTION SCORE ^a 40K IDLA 1.25% N=6 | | | | | | | | | | | | | |
| MEAN | 1 | 1 | 0.8 | 0.8 | 0.5 | 0.3 | 0.7 | 0.8 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| (SE) | (0) | (0) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0) | (0) | (0) | (0) | (0) |
| RANGE | 1,1 | 1,1 | 0,1 | 0,1 | 0,1 | 0,1 | 0,1 | 0,1 | 1,1 | 1,1 | 1,1 | 1,1 | 1,1 |

^a EVALUATED ON A SCALE OF 0-1, WITH 1="YES"(A CHANGE IN TEMPERATURE WAS PERCEIVED), AND 0="NO" (NO CHANGE IN TEMPERATURE WAS PERCEIVED).

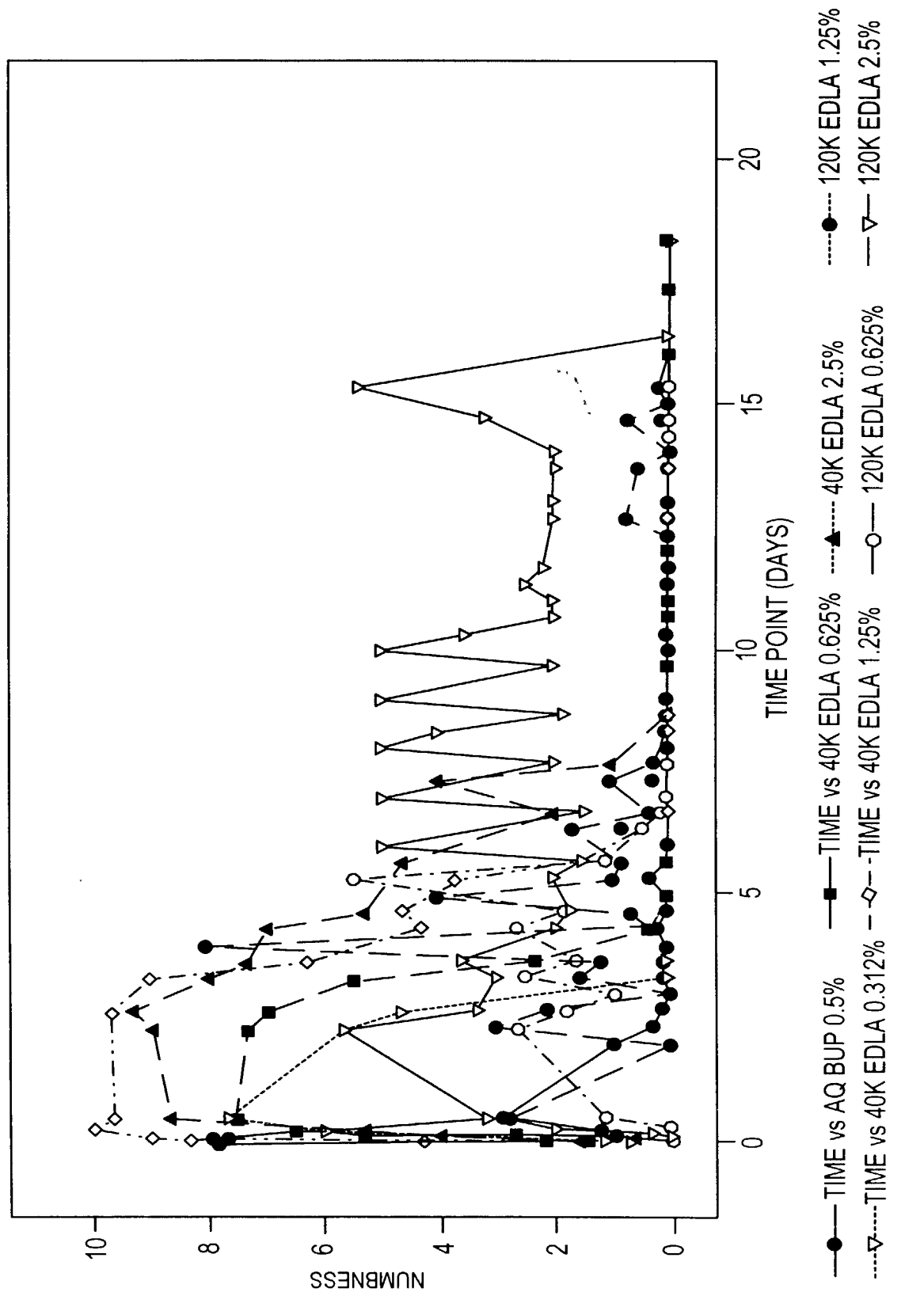
^b EVENING SCORE.

MEAN (SE) SCORES OF TEMPERATURE PERCEPTION FOR 1.25% 40K EDLA vs 1.25% 40K IDLA

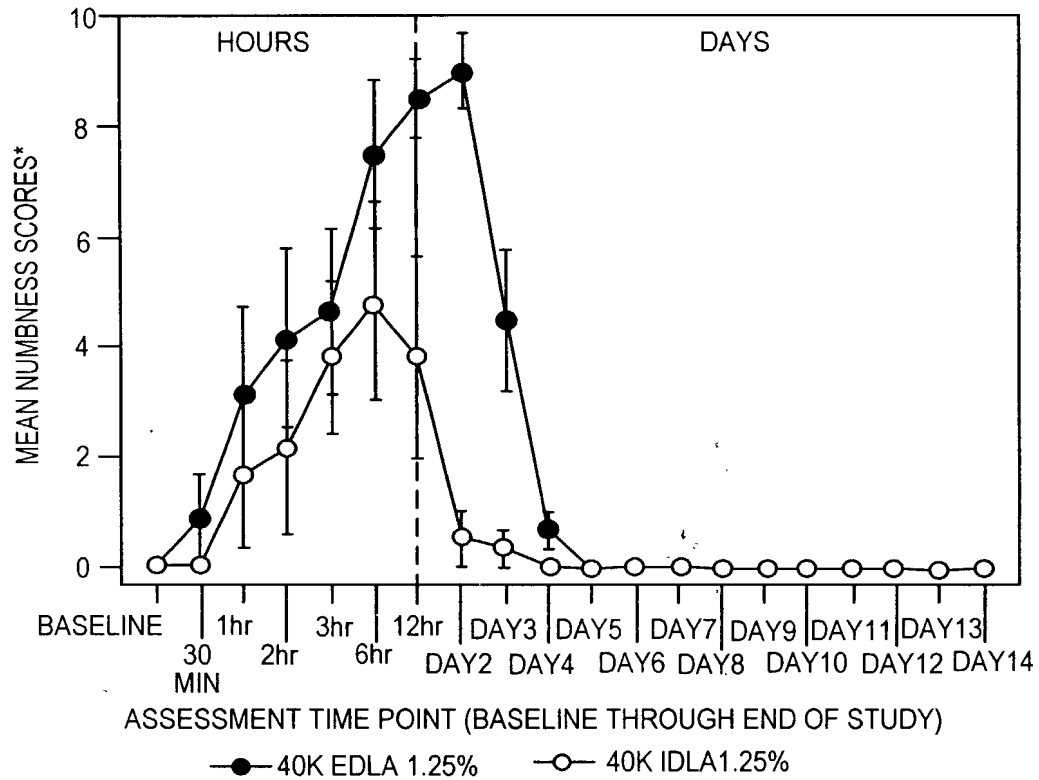
FIG. G5

FIG. G6

MEAN LEVEL OF NUMBNESS OVER TIME FOR TREATMENTS COMBINED - TOP OF FOOT PART I



52/57



| | BASE-LINE | 30 min | h1 | h2 | h3 | h6 | h12 | DAY 2 ^b | DAY 3 ^b | DAY 4 ^b | DAY 5 ^b | DAY 6 ^b | DAY 7 ^b |
|----------------------------------|-----------------------|--------|-------|-------|-------|-------|-------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| LEVEL NUMNESS SCORE ^a | | | | | | | | | | | | | |
| | 40K EDLA 1.25% N=6 | | | | | | | | | | | | |
| MEAN | 0 | 0.8 | 3.2 | 4.2 | 4.7 | 7.5 | 8.5 | 9.0 | 4.5 | 0.7 | 0 | 0 | 0 |
| (SE) | (0) | (0.8) | (1.6) | (1.6) | (1.5) | (1.4) | (0.7) | (0.7) | (1.3) | (0.3) | (0) | (0) | (0) |
| RANGE | 0 | 0,0.5 | 0,10 | 0,10 | 0,10 | 2,10 | 6,10 | 6,10 | 0,8 | 0,3 | 0 | 0 | 0 |
| LEVEL NUMNESS SCORE ^a | | | | | | | | | | | | | |
| | 40K IDLA 1.25% N=6 | | | | | | | | | | | | |
| MEAN | 0 | 0 | 1.7 | 2.2 | 3.8 | 4.8 | 3.8 | 0.5 | 0.3 | 0 | 0 | 0 | 0 |
| (SE) | (0) | (0) | (1.3) | (1.6) | (1.4) | (1.8) | (1.8) | (0.5) | (0.3) | (0) | (0) | (0) | (0) |
| RANGE | 0 | 0 | 0,8 | 0,10 | 0,10 | 0,10 | 0,10 | 0,3 | 0,2 | 0 | 0 | 0 | 0 |

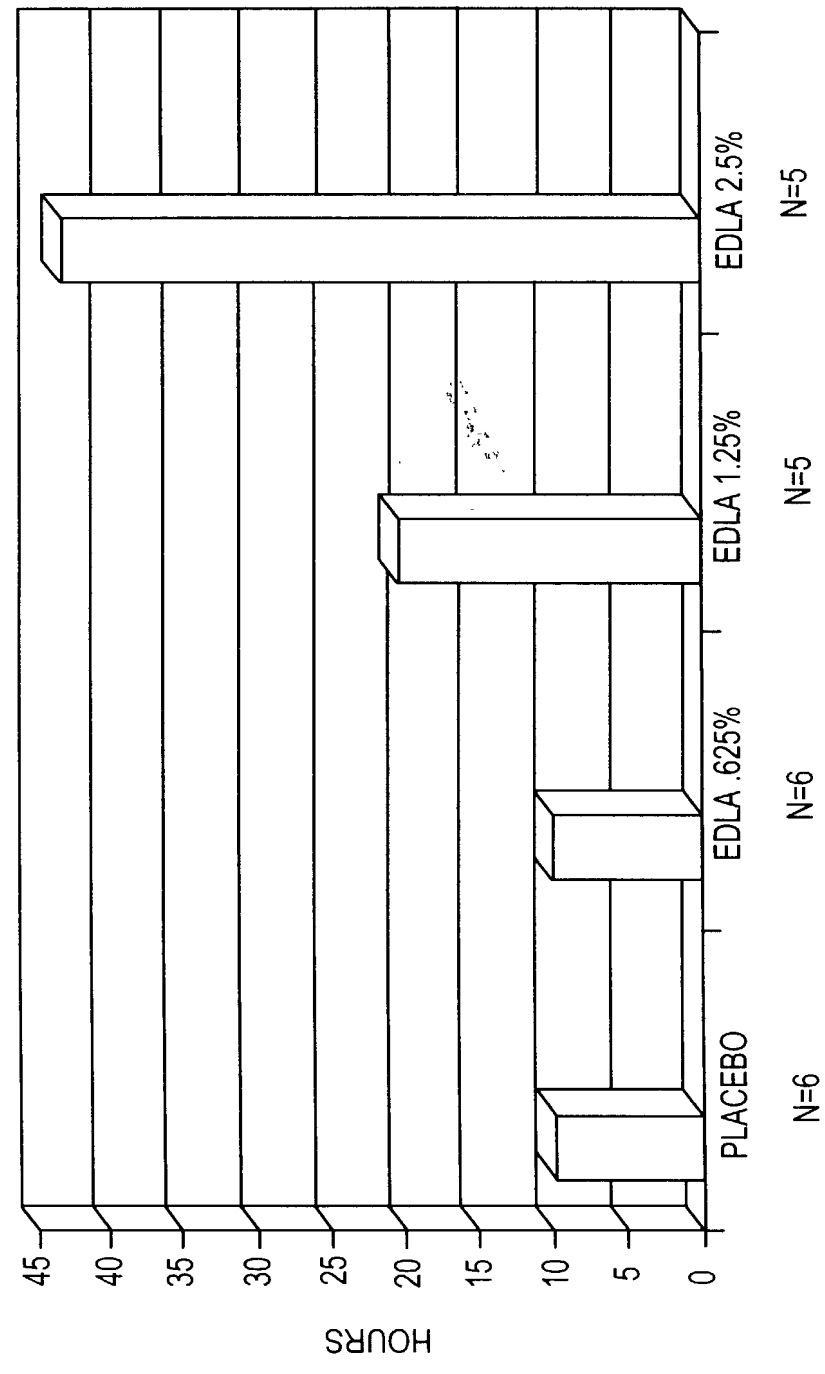
^a EVALUATED ON A SCALE OF 0 -10, WITH 0=NOT NUMB AT ALL, AND 10=TOTALLY NUMB.

MEAN (SE) NUMNESS SCORES FOR 1.25% 40K EDLA vs 1.25% 40K IDLA

FIG. G7

FIG. H1

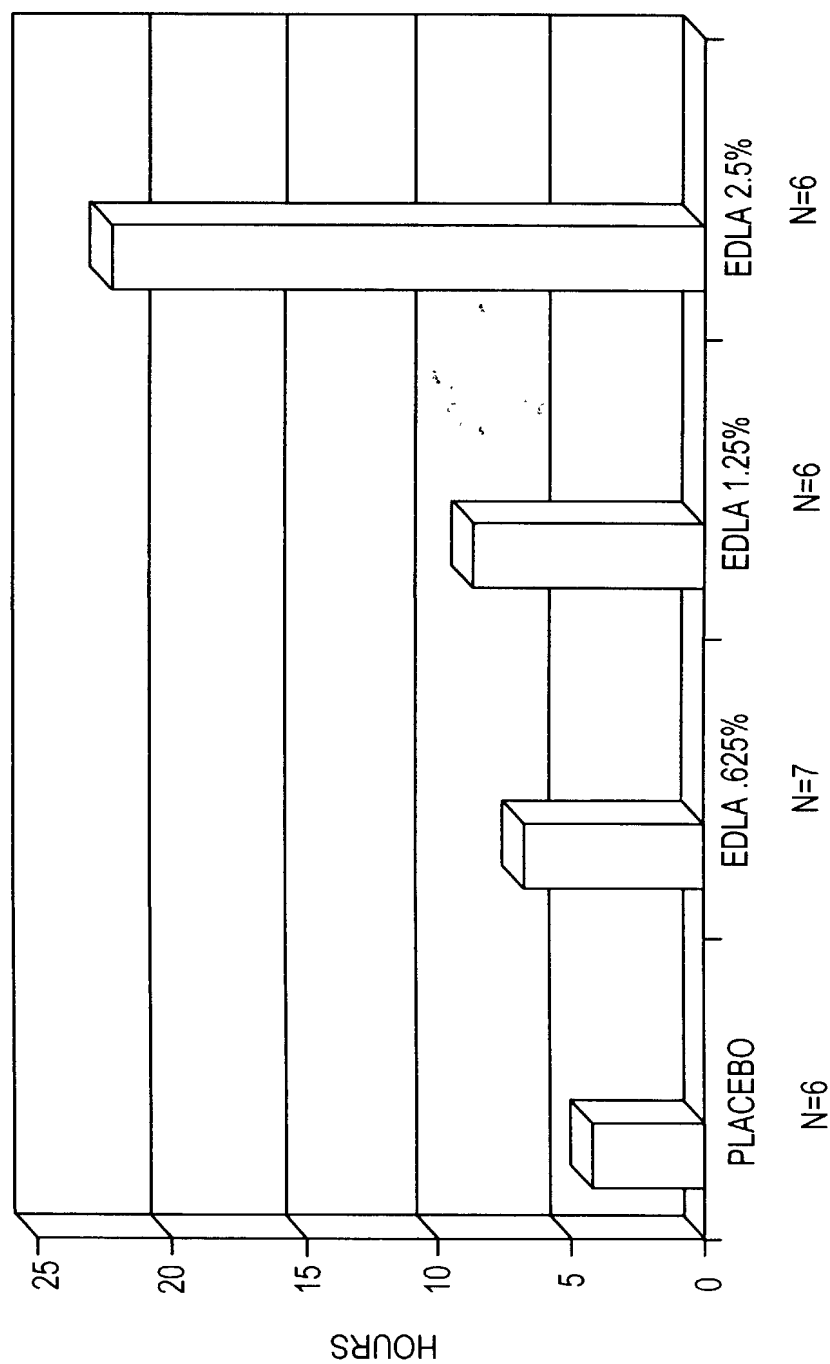
MEDIAN TIME TO FIRST PAIN>3 (ITT)



LOG RANK TEST, p=0.0498

FIG. H2

MEDIAN TIME TO FIRST RESCUE (ITT)



LOG RANK TEST, $p=0.0032$

55 / 57

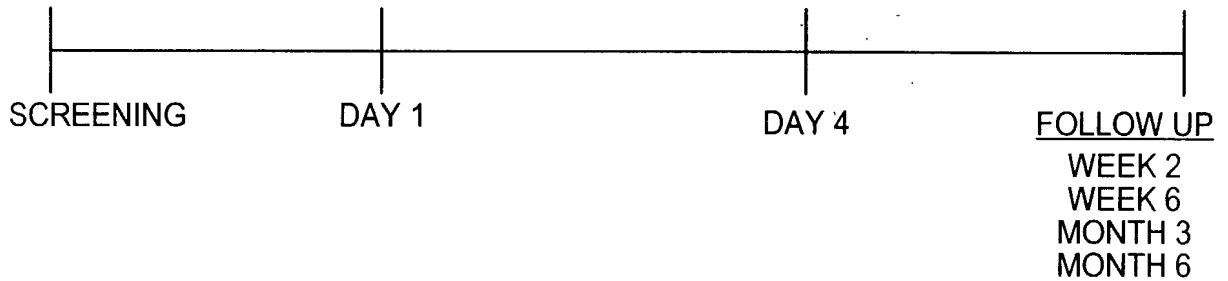
PART: 1

MICRODIALYSIS STUDY DESIGN

15 mL 40K EDLA 2.5% (L)
N=4

15 mL 40K EDLA 2.5% (R)
15 mL 40K EDLA 2.5% (L)
N=4

15 mL 40K AB 0.5% (R)
15 mL 40K AB 0.5% (L)
N=4



PART: 2

7.5 mL 40K EDLA 2.5% (R)
7.5 mL 40K EDLA 2.5% (L) N=6

15 mL 40K EDLA 2.5% (R)
15 mL 40K EDLA 2.5% (L)
N=6

15 mL AB 0.25% (R)
15 mL AB 0.25% (L)
N=4

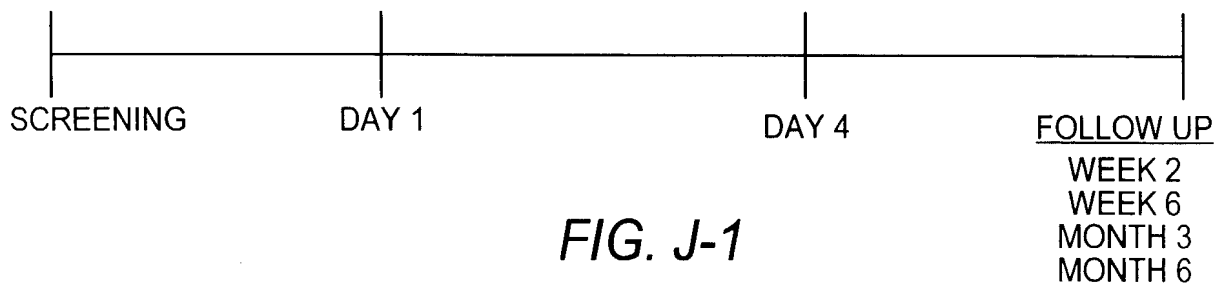


FIG. J-1

56 / 57

INJECTION AND PROBE PLACEMENT

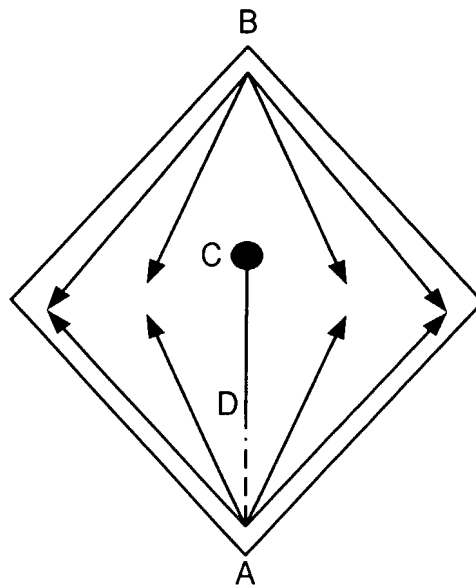


FIG. J-2

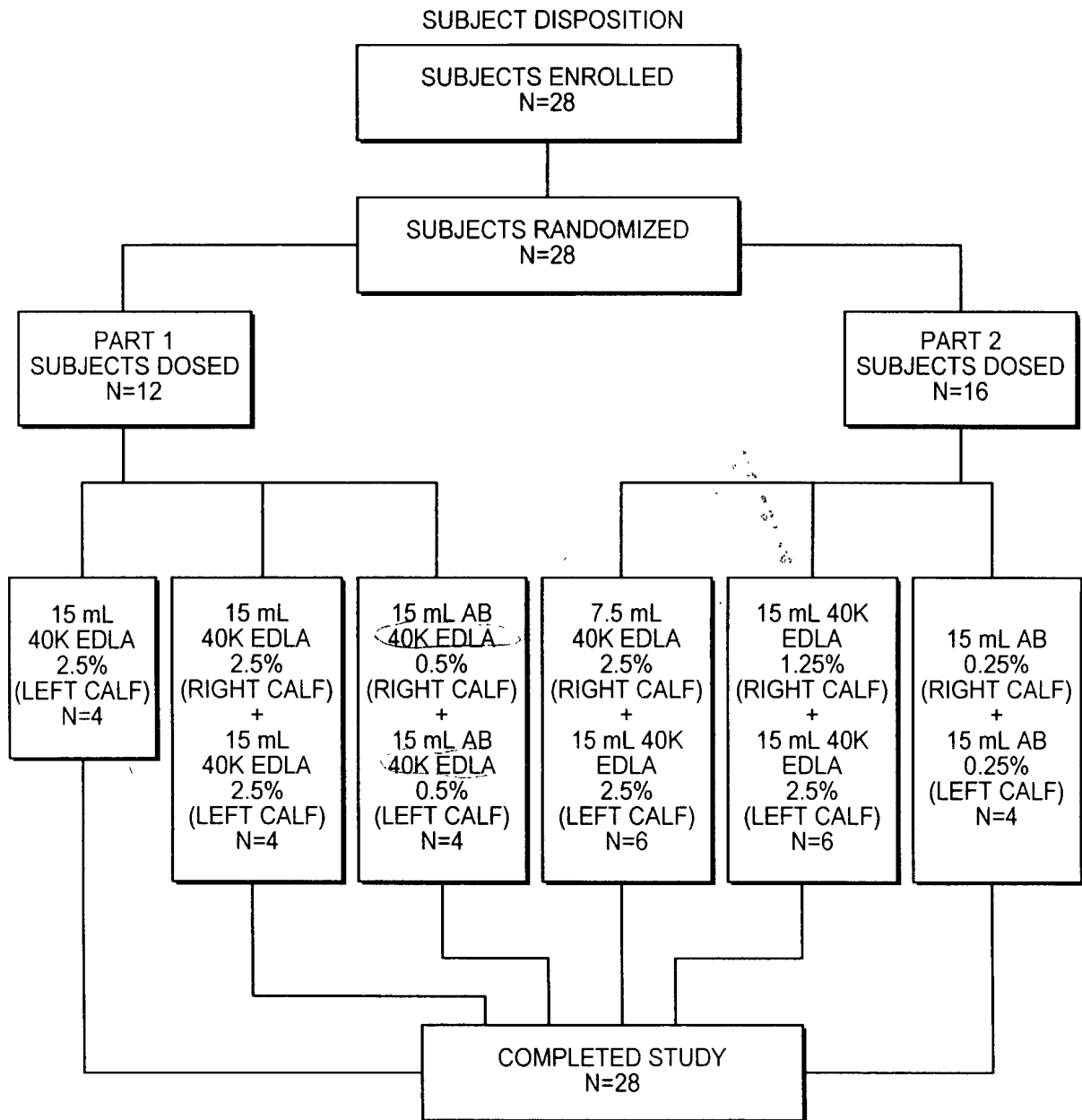


FIG. J-3